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GUT ENDOCRINE TUMORS

On the classification, diagnosis, and treatment,
with special reference to midgut tumors



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by

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The present thesis is based on the following papers:

- I. Carcinoid tumors in the gastrointestinal tract - an analysis of 156 cases. H Mårtensson, A Nobin and F Sundler.
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- II. Endocrine tumors of the ileum - cytochemical and clinical aspects. H Mårtensson, A Nobin and F Sundler.
In manuscript.
- III. Elevated concentrations of substance P and 5-HT in plasma in patients with carcinoid tumors. P Emson, RFT Gilbert, H Mårtensson and A Nobin.
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- IV. Angiographic and computed tomographic appearance of secondary carcinoid of the liver. M Sako, A Lunderquist, T Owman, H Mårtensson and A Nobin.
Cardiovasc Intervent Radiol 5:90-96, 1982.
- V. Selective mesenteric vein catheterization and plasma serotonin determination in patients with carcinoid tumors. A Nobin, S Axelsson, B Falck, S Ingemansson, A Lunderquist, H Mårtensson and W Reichardt.
World J Surg 7:223-229, 1983.
- VI. Temporary liver dearterialization in patients with metastatic carcinoid disease. S Bengmark, M Ericsson, A Lunderquist, H Mårtensson, A Nobin and M Sako.
World J Surg 6:46-53, 1982.
- VII. Embolization of the liver in the management of metastatic carcinoids. H Mårtensson, A Nobin, S Bengmark, A Lunderquist, T Owman and G Sandén.
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In the text the above articles are referred to by their Roman numerals.

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Science is always in parenthesis; poetry is not

John Fowles

INTRODUCTION

The endocrine tumors of the gastrointestinal tract comprise a heterogeneous group of tumors that has attracted a great interest through the years and still is studied intensely. One of the reasons for this interest is that some tumors give rise to specific symptoms and that these sometimes may be correlated with the content of peptides and amines in the tumor and circulating blood. Other reasons for the interest are the challenge in diagnosis and treatment of these tumors. By successful treatment cure is obtained both from the tumor and the symptoms. The effects of excessive secretion of amines and peptides by the tumors may also be studied in order to understand the physiological functions of the substances. Thus, gut endocrine tumors represent a category of tumors that deserves close analysis using radioimmunoassay, cytochemistry and electron microscopy in addition to routine histology. Furthermore, clinical data may be correlated to findings obtained with these methods and thus increase the understanding of why some histologically identical tumors can have a totally different clinical course.

Classification

In 1838 Merling (123) reported on an appendiceal tumor that is considered to be the first description of a carcinoid tumor. The first report on an ileal carcinoid was published by Langhans (98) in 1867 but the first detailed description of both macroscopic and microscopic features was published by Lubarsch (106) in 1888. Two years later Ransom (154) reported the first metastatic carcinoid tumor originating in the ileum. In spite of this the tumor was considered to be benign, and in 1907 Oberndorfer (36, 137) coined the term carcinoid to stress the assumed benign nature of the tumor. He emphasized five major features of the tumor:

1. It is a small tumor and quite often multiple.
2. The cells are mostly arranged in an undifferentiated growth pattern, but sometimes in a hint of glandular growth pattern.
3. No infiltrative tendency.
4. No metastases.
5. Slowly growing and not reaching any substantial size, therefore its nature is harmless.

This concept was not questioned until 1949 when Pearson (146) showed the malignant potency of the carcinoid tumor.

The "classical" carcinoid concept, as defined by Oberndorfer (136, 137), covers most gastrointestinal endocrine tumors. Whether this

definition is the best or most relevant will be discussed later, but it is the one that most pathologists still use. Hence, clinicians are familiar with it and almost all clinical reports on patients with a carcinoid tumor define the tumor this way. Oberndorfer's assumption that the carcinoid is a benign tumor has prevailed over the years, even if Pearson (146) pointed out in 1949 its malignant nature. The five-year survival rate has in several studies been shown to be 50-99 % (61, 130), but when distant metastases were present the rate was drastically reduced to less than 20 %.

Argentaffinity. Since the first descriptions of the carcinoid by Lubarsch (106) and Oberndorfer (136, 137), ideas about the histogenesis of the tumor have been changing. The first theory was published in 1914 when Gosset and Masson (65) showed, by demonstrating the argentaffinity of the tumor, that the carcinoid originated from Kultschitzky cells occurring within the intestinal epithelium. This argentaffin reaction is a direct reduction of silver salts by the cell granules. In 1928 Masson (119) proposed the nomenclature of argentaffin-cell tumor.

The carcinoid syndrome was first described by Cassidy (31, 32) in 1930 but it was not until 1954 when Thorson et al (183) analyzed 16 patients that the connection between the syndrome and the hyperserotoninemia was recognized. The interpretation was that the symptoms were due to the hyperserotoninemia (147), as the tumor had been shown to contain and release serotonin (101). Furthermore, an increase of urinary 5-hydroxyindoleacetic acid (5-HIAA), the metabolite of oxidative deamination of serotonin, was pointed out (142).

At this time a solid concept of the carcinoid seemed to be established by morphology (136, 137), histochemistry (119), biochemistry (101, 142, 147) and clinical signs (193). However, new observations disturbed the concept. Several other endocrine tumors turned out to be non-argentaffin. Patients with these tumors also showed an increase of urinary histamine and serotonin, evidence of urinary 5-hydroxytryptophan, and a different type of flushing (169). In addition, it was demonstrated that argentaffin tumors released histamine and kinins (135, 174).

Argyrophilia. However, a common feature of both non-argentaffin and argentaffin tumors was that they displayed argyrophilia in the tumor tissue. The argyrophil reaction is a two step reduction of silver salts by the cell granules. Tissue is first treated in a reducing solution so that the granules are in a reduced state and hence capable of acting as an oxidizing agent. The granules can thereafter reduce silver salts to metallic silver. As the increasing knowledge about the tumors confused the carcinoid concept, Williams and Sandler (203) in 1963 suggested a classification of foregut, midgut and hindgut tumors based on the embryologic sites of origin. Tumors arising from the bronchus, stomach, pancreas and the first part of duodenum are foregut

derivatives. Small intestine from the mid-duodenum, together with the caecum and colon as far as the mid-transverse colon form the midgut. The hindgut comprise the rest of colon and rectum.

APUD cells. By the embryologic classification endocrine tumors of the pancreas and rectum were also included in the carcinoid category. These tumors, however, are quite different in their clinical appearance than midgut tumors and later discoveries have revealed great differences in cell content of neurohormonal peptides and amines. Subsequently numerous observations concerning ultrastructure, cytochemistry and biochemistry of the tumor have been reported. Furthermore, it has been claimed that endocrine cells of the gut are cells (APUD) with a specific ability to synthesize monoamines from an amine precursor and originate from the neural ectoderm (143). However, there are now some doubts about the origin of the cells and the precursors. Andrews (11, 12) has shown the development of endocrine cells in a series of in vitro experiments with endoderm and mesoderm from quail and chick embryos. This implies that not all APUD cells are neural crest derivatives.

Diagnosis

The carcinoid tumor was considered almost harmless for years, but due to several studies (76, 125, 146, 165) the malignant features are now well recognized. Unfortunately, so far, no symptom or diagnostic procedure has sufficient specificity and sensitivity for the screening of carcinoid tumors. The excretion of 5-hydroxyindoleacetic acid (5-HIAA) in urine has been claimed to be a good tool for the diagnosis of gastrointestinal carcinoids (42, 74), but gastric and rectal carcinoids usually have normal levels of 5-HIAA in urine (192) regardless of size and spread. This may also be the cases with metastatic ileal tumors. Angiography of the small bowel and liver is valuable (27, 42) but it is a too complicated investigation for screening purposes. The carcinoid syndrome has been claimed to be provoked by catecholamines (103), alcohol (1), calcium (88) and pentagastrin (56), but so far all patients tested had a known metastatic disease. In light of these diagnostic difficulties it is not surprising that Moertel (125) reported 30 different clinical diagnoses in 56 patients with symptomatic small bowel carcinoid tumors.

By the growing knowledge about tumor amine and peptide contents attempts have been made to correlate this to circulating levels of the substances. In the case of pancreatic tumors many of them secrete peptides that are measurable in plasma and exhibit specific symptoms (Table I).

In order to refine the diagnosis and the exact localization of pancreatic tumors transhepatic portal venous catheterization with selective venous blood sampling from the pancreatic veins (157) has been successfully performed. By the same technique, but with sampling from the splanchnic veins, tumors from the small bowel or lymph node meta-

stases may be detected (156). In addition, sampling from hepatic veins may detect liver metastases.

Table I. Pancreatic endocrine tumors with specific symptoms

Clinical syndrome	Peptide
The ulcerogenic syndrome	Gastrin
The hypoglycemic syndrome	Insulin
The hyperglycemic, cutaneous syndrome	Glucagon
The diarrheogenic syndrome	VIP

Treatment

In several retrospective studies (15, 76, 125, 130, 191, 192) it has been shown that 30-50 % of the carcinoid tumors had metastasized at the time of diagnosis. This fact, together with the poor survival rate in patients with distant metastases, makes it imperative to be as radical as possible at surgery.

The primary tumor should always be removed and as much as possible of the metastases. After the primary operation a transhepatic portal venous catheterization with blood sampling may detect and localize remnant tumor tissue.

In order to lessen patients' suffering from the carcinoid syndrome medical therapy against flushing and diarrhea has been tried with no success. Cytotoxic drugs also seem ineffective in controlling symptoms and tumor growth (70, 128, 129, 214). Recently, however, one report has shown good effect on symptoms, but not on tumor growth, with Interferon (211). The best results, however, have been obtained by different surgical procedures including liver resection (17, 41, 204), enucleation of liver metastases (184), hepatic artery ligation and hepatic dearterialization (14, 78, 79, 120). Embolization of the liver also seems to be useful (3, 26, 107, 151). However, most series contain only a few cases and some are combined with a review of the literature. The treatment of pancreatic tumors is somewhat different from that of the other gastrointestinal endocrine tumors. Some of the tumors respond at least partially to treatment with streptozotocin (214), and the Zollinger-Ellison syndrome may be controlled by H_2 -blocking agents (28). The surgical approach, however, aiming at removal of the primary tumor and metastases is principally the same as for gastrointestinal endocrine tumors.

THE AIMS OF THE STUDY

The aims of the present study are to investigate:

1. the clinical and biochemical characteristics of patients with carcinoid tumors treated in our hospital during a 35-year period,
2. the occurrence and distribution of neurohormonal peptides and amines in endocrine tumors of the lower small intestine,
3. if certain characteristics of the tumors such as growth pattern, hormone content and primary tumor size correlate to the malignant potential,
4. the identity of the substance P-like immunoreactivity in human plasma,
5. the correlation between the tumor content of neurohormonal peptides and amines and the plasma levels of corresponding substances,
6. the diagnostic specificity regarding the existence of carcinoid tumor tissue of angiography, computed tomography and abdominal vein catheterization with blood sampling for serotonin assay,
7. the value of serotonin determination in platelet-poor plasma and whole blood for the diagnosis and localization of carcinoid tumors,
8. the therapeutic value of temporary liver dearterialization and liver embolization in the management of patients with metastatic carcinoid disease.

MATERIAL AND METHODS

In paper I a retrospective study of 156 patients with gastrointestinal endocrine tumors was performed. The diagnosis was histopathologically based on sections stained with hematoxylin and eosin. Most specimens were also stained with silver according to Masson. The analysis consisted of age, symptoms, clinical features, clinical diagnosis, patient's and doctor's delay, tumor size, multicentricity, tumor distribution, metastases, additional primary neoplasms of other types and survival. In addition, two foregut and four hindgut tumors were re-examined using immunocytochemistry for the demonstration of neurohormonal peptides and the Falck-Hillarp histofluorescence technique for the demonstration of intracellular amines.

In paper II 16 patients with ileal carcinoid tumors and liver metastases were analyzed regarding clinical data, biochemistry, tumor size, multicentricity and histopathological growth patterns. Immediately after surgery all tumors were frozen, freeze-dried, fixed by exposure to vaporous formaldehyde or diethyl-pyrocabonate and embedded in paraffin in vacuo. The prepared specimens were then processed for immunocytochemical demonstration of neurohormonal peptides. The presence of serotonin was shown by formaldehyde-induced fluorescence.

In paper III 10 patients with ileal carcinoid tumors and liver metastases were investigated. Blood was collected from peripheral and hepatic veins for determination of serotonin in whole blood and platelet-poor plasma and substance P-like immunoreactivity in plasma. The serotonin was measured by high performance liquid chromatography and electrochemical detection. Substance P-like immunoreactivity was determined by radioimmunoassay using N- or C-terminally directed antibodies.

In paper IV the angiographic appearance of liver metastases from carcinoid tumors in 27 patients was studied. The primary tumor was ileal in 25 cases and jejunal and rectal in one case each. Liver angiograms were analyzed in all patients for distribution, size, degree of vascularity and patterns of tumor staining. Computed tomography scans were evaluated in 13 patients concerning the distribution and size of the metastases before and after intravenous bolus contrast administration.

In paper V 10 patients were analyzed regarding serotonin in blood samples from different abdominal blood vessels and a peripheral vein for the localization of the carcinoid tumors. Five patients with pancreatic gastrinomas were used as a reference group for the abdominal samples and 22 healthy persons constituted controls for the peripheral samples. The abdominal vein samples were obtained by a percutaneous transhepatic puncture of the portal vein and manipulation of the portal catheter to different branches of intestinal and

pancreatic veins. Serotonin was then determined in a platelet-poor plasma fraction by an enzymatic procedure.

In paper VI 16 patients with liver metastases from ileal carcinoid tumors were treated with temporary liver dearterialization. The operation consisted of careful dissection after which the only structures attaching the liver were the hepatic artery, the common bile duct, and the portal and the hepatic veins. Two nylon strings were placed around the hepatic artery distal to the gastroduodenal artery, threaded through two catheters and taken out through separate incisions in the abdominal wall. Cholecystectomy was always performed to avoid the risk of gallbladder necrosis during the dearterialization. After 3-4 days the strings were pulled tight for 16 hours and then removed. The effect of the treatment was evaluated by arteriographies and biochemical changes as well as the clinical signs and symptoms. Liver function tests were monitored in all patients and most were followed with determination of serotonin in platelet-poor plasma and 5-HIAA in urine. The serotonin determination was performed with high performance liquid chromatography with electrochemical detection, and 5-HIAA in urine was measured by a spectrophotometric method.

In paper VII 8 patients with liver metastases from ileal carcinoid tumors and suffering from the carcinoid syndrome were treated with embolization of the liver. All patients had previously undergone cholecystectomy. Depending on the vascular anatomy the embolization was performed with a catheter placed in the proper hepatic artery or selectively in the right and left hepatic arteries. The embolic material consisted of a mixture of gelatin foam powder, contrast medium and an antibiotic. The effect of the treatment was evaluated every 3 months by clinical improvement, angiographic changes in tumor mass and biochemical changes. Serotonin was measured in platelet-poor plasma and whole blood with high performance liquid chromatography with electrochemical detection. Excretion of 5-HIAA in urine was measured by a spectrophotometric method.

Comments on methods

Details on the methods used are presented in the particular papers, but some methods and their possible pitfalls require further discussion here.

Immunocytochemistry. The indirect immunofluorescence technique (36) and the peroxidase-antiperoxidase (PAP) procedure (185) have been used. The outline of both methods is shown in Fig 1. They are well recognized and widely used. The advantage of the PAP-technique is that much higher dilutions of antisera are used and that PAP-stained specimens can be preserved. On the other hand, the PAP-technique is more complicated and time-consuming and serotonin cannot be demonstrated by this procedure. In addition, some of the reagents are considered to be carcinogenic. All techniques dealing with immunoreactions require

refined handling of the sample and the reagents. If the sample is not handled under optimal conditions the peptide or the antigenicity of the peptide may be lost and thus give false negative results. The antiserum may be directed against only a few amino acids causing cross-reactions with other peptides. The antiserum also may be raised to a contaminated antigen, resulting in a reaction with contaminants and not the peptide intended. It is therefore important to use antisera with well-known characteristics.

IMMUNOFLUORESCENCE TECHNIC



IMMUNOPEROXIDASE TECHNIC

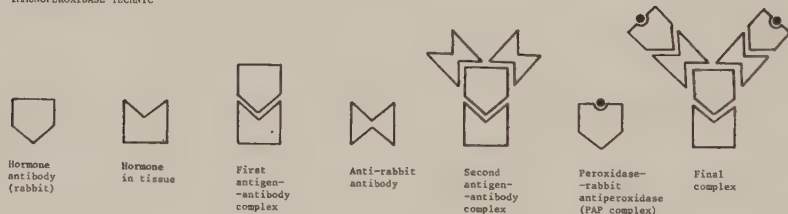


Fig. 1. The outline of the immunofluorescence technic and the peroxidase-antiperoxidase procedure.

Fig 1. The outline of the immunofluorescence technique and the peroxidase-antiperoxidase procedure.

Serotonin analysis. Blood samples for the analysis of serotonin in platelet-poor plasma (PPP) and whole blood were collected in ice-chilled tubes containing EDTA and ascorbic acid. For the analysis of PPP the samples were centrifuged twice resulting in an average platelet count of $10 \times 10^6/l$ plasma compared to the normal $170-300 \times 10^6/l$ plasma.

Serotonin in PPP was analyzed both by an enzymatic procedure and high pressure liquid chromatography (HPLC). Whole blood samples were analyzed by the HPLC method.

The enzymatic procedure was used in the first part of this study and

the results were consistent with those obtained with the HPLC. The latter technique, however, has advantages such as high sensitivity, no known interference, excellent linearity and small intra-assay variations. The HPLC also permits analysis of several metabolites simultaneously.

The value of measuring serotonin in PPP has been debated, and some deny the existence of a free pool of serotonin in plasma. The levels measured would instead be a reflection of serotonin released from destroyed platelets. In our hands, however, the measurement of serotonin in PPP is a very reliable and reproducible technique. The extremely small variations (0.4-4.8 ng/ml) in normal persons show that the technique does not cause platelet damage. Thus, there seems to be a free pool of serotonin in plasma enabling an accurate measurement.

Substance P analysis. Blood samples for the analysis of substance P in plasma were collected in glass tubes containing saline, parachloromercuribenzoic acid, EDTA and ascorbic acid.

Most substance P antisera used show varying degrees of cross-reactivity towards C-terminal fragments of substance P. This makes the interpretation of the results difficult. In this study we used an antiserum specific for the N-terminal part of substance P. This antiserum showed only 0.1 % and 0.01 % cross-reactivity with SP₂₋₁₁ and SP₃₋₁₁, respectively. It did not cross-react at all with the smaller C-terminal fragments, eledoisin, physalaemin, or bradykinin.

In the radioimmunoassay for substance P, antibodies directed either to the N- or C-terminal of the antigen were used. Serial dilution and separation on a HPLC column were used to show the resemblance to undeca peptide substance P. The analysis thus permitted accurate and specific measurements of a substance identical to the synthetic undeca peptide substance P.

RESULTS AND COMMENTS

General aspects

Incidence. The real incidence of endocrine tumors in the gastrointestinal tract is not known. Most reported tumors are incidental findings at surgery or necropsy and not the result of a planned investigation. There is a wide variation in incidence in different necropsy series (111, 125, 146, 149, 152). One of the best studies, however, comes from Malmö (21), with a stable population served by one hospital and a high necropsy rate. In 16,294 autopsies during a 12-year period 199 endocrine tumors were found. This makes the incidence 1.22 %. Combining these data with the surgically diagnosed tumors, the authors of this study, Berge and Linell (21) could report an average annual incidence of 8.4 per 100,000 inhabitants, which is much higher (seven times) than the incidence recorded by the National Cancer Register in Sweden. The real incidence most likely is at least as high as that reported in the Malmö study, but the figure is probably of little clinical importance since most tumors are found at necropsy (about 90 %) in patients who have died with the tumor and not because of it.

Site. The distribution of the endocrine tumors varies from study to study, usually due to small numbers and different populations (18, 68, 96, 130, 165, 192). Another bias might be the tendency to discover and report metastatic and symptomatic tumors rather than the silent, small primary tumor (61). There are, however, some collective reviews, each consisting of approximately 3,000 cases (61, 140, 167, 206). Some cases are naturally reported in more than one of the above papers, but jointly the figures show approximately 45 % of the tumors in appendix, 30 % in ileum, 15 % in rectum and 2 % each in the stomach, duodenum, Meckel and colon. In our study (I) the proportion of ileal tumors is high (54 %), reflecting that many cases with this tumor are referred to us for further work-up and treatment.

Age. The carcinoid may be found in all ages. In children and young adults, almost all tumors are of appendiceal origin (52). The youngest patient reported was 10 days old (54). The average age for patients with appendiceal tumors is in the mid 30s (60, 61, 127). This corresponds to the average age at which appendectomies often are performed. The average age of patients with non-appendiceal tumors is the mid 50s (20, 61, 96, 121, 125, 174). Our findings (I) are in accordance with these figures but it must be pointed out that the patients in the autopsy group were naturally older.

Sex. There are no reports on sex differences, except that carcinoids in the appendix are more frequent in women. This can probably be explained by the fact that women more often than men have pelvic operations including en passant appendectomy. In our series (I) 15 of 17 incidental appendectomies were performed on women.

Multiplicity. According to the site of the primary tumor the multiplicity varies in different reports (61, 96, 116, 125, 130, 165, 186), but it seems as if one third of the ileal carcinoids are multicentric. Our findings (I) agree with this finding as, out of 91 ileal carcinoids, we report 37 multiple tumors. The multicentricity can occur in different parts of the gastrointestinal tract (61), and Moertel (125, 127) has found another carcinoid tumor in 4.2 % of patients with appendiceal carcinoid tumors. This fact might explain why some carcinoids in the appendix have metastases.

Associated malignant neoplasms. The carcinoid tumor may not only be multiple, but also associated with another malignant neoplasm. The incidence varies from 17 to 53 % (21, 61, 92, 96, 125, 130, 146, 186, 196, 211). In our study (I) we found other neoplasms in 14 % of the clinical cases and in 36 % of the autopsies. With more extensive necropsies the incidence probably would have been higher as the carcinoid tumor probably grows slowly and thus allows simultaneous growth of other neoplasms.

Metastases. The incidence of metastases varies to a great extent according to how the materials are collected. In several studies, however, the incidence seems to be correlated to the size of the primary tumor (16, 96, 125, 130, 211) and our findings (I) support this. Furthermore, we found that, of 91 midgut carcinoids 42 had liver metastases while 24 had lymph node metastases only at the time of diagnosis. In clinical series the incidence of metastases is higher than in necropsies, and Moertel (125) found that, of 56 patients with symptomatic tumors, 48 had lymph node metastases and 22 had liver metastases. In our series (I) of midgut tumors we found no metastases in 13 %, lymph node metastases in 20 % and liver metastases in 67 % of our clinical patients. Our autopsy series contained no metastases in 57 %, lymph node metastases in 40 % and liver metastases in 3 %. This illustrates some of the problems the clinician has to deal with when he outlines the treatment for a patient with a carcinoid tumor.

Signs, symptoms. Most carcinoid tumors are asymptomatic. Many of them are detected by incidence at necropsy or surgical intervention for unrelated conditions (125). In our series (I) we found 18 different clinical diagnoses in 61 patients with midgut tumors. Some of them were of course correct when the carcinoid was an incidental finding, but many reflect the unspecific signs and symptoms of the tumor even in an advanced stage. The most common main clinical symptom was diarrhea, abdominal pain or intestinal obstruction at the time of diagnosis. Pain and obstruction were almost the only initial symptoms in Moertel's series of 56 symptomatic tumors (120), but gradually diarrhea, loss of weight, and vomiting occurred. None of these symptoms is specific for the carcinoid, and this makes it difficult for the doctor in the diagnostic procedures. In our series (I) the delay exceeding 2 years and attributable to the doctor was 30 %. Some specific symptoms constitute the carcinoid syndrome (97). The main

symptoms are flushing, diarrhea, abdominal cramping, tricuspid insufficiency and pulmonary stenosis, asthmatic dyspnoea and loss of weight. The liver is, due to a massive metastatic growth, frequently palpable (41). Liver metastases are mandatory for the syndrome to appear except in large bronchial carcinoids and ovarian or testicular teratomas (41) where the venous drainage goes directly into the systemic circulation. However, there are reports on patients with the carcinoid syndrome and elevated serotonin levels with no liver metastases palpable at laparotomy (51, 84). Whether these reports are valid or not is hard to say, but sometimes the metastases are very small (IV) and difficult to palpate.

The incidence of carcinoid syndrome in patients with carcinoid tumors seems to be low. According to Spann et al (182) approximately 210 cases are reported, and most of them originate in the small bowel. There are, however, reports on primary tumors from the whole gastrointestinal tract causing carcinoid syndrome (34, 37, 41, 102, 115, 166, 182). One disturbing factor in almost all reports is the lack of a clear definition of the carcinoid syndrome. The only exception I have found was in a report by Davis et al (41) who defined the syndrome as a combination of a histologically verified malignant neoplasm and abnormally increased urinary excretion of 5-HIAA. It seems as if other investigators equate flushing with the syndrome and, if the flush is missing, a combination of at least two of the other symptoms constitutes the definition. In the present dissertation flushing and/or diarrhea have been used as necessary prerequisites for the term carcinoid syndrome.

Prognosis. The conviction that carcinoid tumors are benign, stated by Oberndorfer (136, 137), may have some support in general survival figures presented in various reports (61, 68, 165, 197) but if the survival rate by site or extent of metastases is used, the picture is darker (15, 61, 96, 125, 130, 191). However, various treatments and uncertainty about correct metastatic staging makes it difficult to evaluate the figures. But there is no doubt about the statement that distant metastases lower the survival rate considerably (61, 125). Our series (I) concurs with this, showing a reduction of 50 % in survival, comparing no metastases and distant metastases in midgut tumors.

Summary of the present study. This study has as distinguished from other studies shown that the delay in diagnosis of a carcinoid tumors mostly depends on the doctor. This is probably due to a combination of a lack in screening tests and the rarity of the tumor, making the doctor unfamiliar with the diagnosis. Regarding other general features such as tumor site, size, multiplicity, metastases and associated neoplasms the study confirms results obtained by other studies. Also the patient age, sex, and prognosis are similar to most reports.

Two foregut and 4 hindgut tumors were re-examined using immunocytochemistry. The results illustrate the multihormonal aspects on tumors arising from the foregut and hindgut.

Classification

Classification of carcinoid tumors can be made by light microscopy, electron microscopy, cytochemistry, biochemistry and by the clinical signs. Another possibility is to use the embryonic division of the gut and hence classify the tumors according to site (203). Additional types of classification are based on the proposed origin of endocrine cells (neuroectodermal) and the ability of the cells to form amines (APUD) (144).

Morphology. The morphology described by Oberndorfer (136, 137) seems to be the only characteristic that is constant in the definition of carcinoids. However, this definition covers many tumors with quite different features concerning growth pattern, cyto- and biochemistry, clinical signs and course.

Embryologic site. The embryologic division of site (foregut, midgut, hindgut) proposed 20 years ago (203) only deals with where the tumor is situated and some clinical and biochemical signs. It is a simple and in most cases useful classification. However, with increasing knowledge of tumor cell content and structure the embryologic classification by site will be less useful.

Growth patterns. The histologic growth patterns have been studied by Soga et al (181) and they found five types (Table II).

Table II. Histological growth patterns according to Soga et al (181).

Type	Characteristic structure
A	Tumors with nodular (insular) solid nests and peripheral invading cords
B	Tumors with a trabecular or ribbon-like structure forming a frequent anastomosing pattern
C	Tumors with a tubular, acinar or rosette-like structure
D	Tumors with structures of lower or atypical differentiation
Mixed	Tumors with mixed structures of any combination of the above

According to these authors the foregut tumors were frequently of the B and mixed types, midgut tumors were of A and mixed types, and hindgut tumors were of the mixed type. The figures in our present study (II) and two previous ones (8, 9) are quite different. The foregut tumors are 50 % of the mixed type and 20 % type D, the midgut tumors are 50 % of type C and 25 % mixed, and the hindgut tumors are 50 % type B and 20 % each of type A and mixed. There are several possible explanations for these differences:

1. The selection of tumors.
2. Different tumors analyzed (primary, lymph node, liver or other metastases).
3. Small series
4. Different definition of the types.

In an attempt to correlate growth patterns and survival, Johnson et al (86) studied 138 carcinoid tumors from patients with known distant metastases. They found that type A and B had the best prognosis of pure growth pattern but the mixed A + B had the best prognosis of all patterns. However, this study does not correlate to site of origin of the primary tumor, and no information regarding the site of origin of the investigated tumor. In our study (II) we found differences in growth pattern between primary tumor, lymph node and liver metastases in the same patient, but in this small series we could not see any prognostic differences based on the growth pattern. It thus might be important to know what kind of tumor is investigated. Another striking feature of both these series is that all patients had an advanced disease which makes both groups selected.

Cytochemistry. The argentaffin reaction of carcinoids shown by Gosset and Masson (65) in 1914 was complemented in the 1950s by the argyrophilia of foregut tumors (83, 104, 169), and by the Grimelius argyrophil reaction (66) of hindgut tumors. Later studies have shown that the majority (if not all) of gut endocrine tumors, including the argentaffin ones, display argyrophilia (198). As the serotonin-containing enterochromaffin cell is the only cell type that reacts with argentaffinity it is thus possible to distinguish between enterochromaffin cells (argentaffin) and other types of endocrine cells (argyrophil) by these reactions (110, 199, 202).

The technique of immunocytochemistry has added a new dimension to the classification of endocrine tumors, by showing the content of different peptides. Several reports have shown that foregut and hindgut tumors are multihormonal (72, 99, 138, 187, 200).

Midgut tumors, however, seem to be more homogeneous in peptide content. Besides serotonin enteroglucagon, gastrin, somatostatin and substance P have been reported in midgut tumors (7, 58, 108, 154, 176, 177, 200, 201).

In our previous reports (8, 9) and in the present study (I) we confirm the previous findings in foregut and hindgut tumors. Most of them were multihormonal and the most frequent peptide was pancreatic polypeptide (10 of 27 and 14 of 25). All 16 midgut tumors contained serotonin, in 15 substance P was present, and in one primary tumor, but not in the corresponding liver metastases we found immunoreactive enkephalin. We thus failed to confirm the findings in other reports of several immunoreactive peptides (108, 200, 201) in spite of an optimal handling of the specimens. This may be due to different types of fixation and/or use of antisera with different specificities. In the present series it is notable that the content of serotonin and substance P in the tumor cells had an equivalent in the patients' plasma. All patients measured had pathological values of serotonin and substance P in plasma (II).

Histogenesis. The most generally accepted hypothesis on endocrine cell genesis is the APUD concept, in which Pearse (143) combined cells distributed throughout the body that all have the ability to synthesize monoamines from a precursor (amine precursor uptake and decarboxylation). The common embryonic origin of these cells was postulated to be the neural crest (144). However, experimental data have shown that many APUD cell types are not of neuroectodermal origin (11, 162). Therefore a redefinition was proposed (145) in which the neuroendocrine-programmed epiblast was claimed to be the source of all APUD cells. With this definition the hypothesis lost its stringency, as all cells of the embryo arise from the epiblast. Furthermore, some cell types included in the latter definition lack the ability to synthesize amines while some exocrine cells such as Paneth, gastric chief and pancreatic exocrine cells, have this ability. Even if the APUD concept may be questioned, it has been and still is a simple and, in broad outline, functional classification.

Summary of the present study. This study has shown that, with optimal handling of the tissue specimens, ileal endocrine tumors are very homogeneous in their amine and peptide contents, almost only storing serotonin and substance P. This is in contrast to other studies claiming the existence also of other neurohormonal peptides.

The histologic growth patterns of the tumors were in this study quite different from other reports. We could notice a difference in growth patterns between the primary tumor and the metastases in ileal endocrine tumors, but no correlation to patient survival. As other studies have not distinguished between the type of tumor and site of origin, their results are difficult to evaluate.

Conclusions on the classification

Since Oberndorfer's "classical" carcinoid concept was coined, many new aspects of the classification have developed. In one sense the carcinoid is synonymous to the endocrine tumor. In many reports on tumors

from various parts of the body the carcinoid diagnosis is made only on routine histopathological examinations. With the new information on amine and peptide content, growth patterns and ultrastructure of the tumor combined with signs and symptoms in the corresponding patient, a new nomenclature is needed. However, the discoveries so far have not been of much value in predicting the proper treatment. The only exception is in some pancreatic tumors. Our findings in midgut carcinoid tumors (II) show that there may be differences between the primary tumor and the corresponding metastases concerning peptide content and growth pattern. This might be a sign of the seriousness of the disease. In that case the aggressiveness in treating patients could be moderated.

In summary, the classification of gastrointestinal endocrine tumors will in the future probably be based on the following features (see also 9):

1. The site of origin.
2. The histopathological features (silver staining, growth pattern, differentiation, ultrastructure, invasiveness and metastases).
3. The content of amines and peptides in the tumor tissue and circulating blood.
4. The association with signs or symptoms of endocrine disorder.

The nomenclature of gastrointestinal endocrine tumors could be based on combinations of the above features, but that would probably create some confusion in the clinical handling. For practical reasons, a simple classification is needed (e.g., site of origin, silver staining or tumor peptide content). From this definition a more refined classification may be made by using the above features for the particular tumor in order to select the best treatment and follow-up.

Diagnosis

Many endocrine tumors remain undetected for years. This is reflected by the fact that most of them have metastases at the time of diagnosis (125) (I), that most patients at the time of correct diagnosis have a different presumed diagnosis (I) or that the carcinoid is an incidental finding (I).

Symptomatology. The carcinoid tumor does not give rise to specific symptoms except when the carcinoid syndrome is present. In several studies (68, 76, 125, 130, 191) including our first study (I) the main symptom was either abdominal pain, obstructive signs or diarrhea. One interesting finding is that the patient early on knows that something is wrong, but the doctor's diagnostic difficulty delays the diagnosis more than two years in 30 % of the cases. When the carcinoid syndrome

is present, there are usually no diagnostic problems except in the rare cases when the primary tumor is not a carcinoid. Cases with hepatocellular carcinoma, pancreatic cancer and thyroid cancer are reported (126, 150) having the carcinoid syndrome.

Biochemistry. The only widely accepted biochemical parameter for the detection of carcinoid tumors is, so far, the urine excretion of 5-HIAA (42). However, it must be emphasized that normal values may be seen in patients with widely spread disease (40, 192) and we have shown that patients with foregut and hindgut tumors may have normal values of 5-HIAA (1). Furthermore, false positive results may be obtained in patients eating bananas, walnuts and other foods containing serotonin. Some drugs containing glyceryl guaiacolate may also produce false-positive-results.

Under normal conditions, almost all circulating serotonin is carried bound to platelets (90). The increased levels of serotonin in PPP in patients with carcinoid tumors have been explained to be an artefact due to platelet aggregation during the preparation of the samples (90). Therefore, measurement of serotonin in whole blood or platelet-rich plasma would more accurately reflect circulating serotonin levels. Others believe that a small, but biologically important portion circulates free in plasma (50). We found that changes in serotonin in PPP after embolization for liver metastases are not uniform with serotonin in whole blood (VII). As the fraction of serotonin is much smaller in plasma than in the platelets, a minor reduction of the total amount is more easily detected in plasma, provided serotonin in PPP reflects better the amount released from the tumor than the total amount. In our hands determination of serotonin in PPP has proved a very reproducible and reliable technique giving valuable information on tumor size and activity.

The serotonin determination in combination with the selective mesenteric vein catheterization has been of great value not only in mapping the tumor extent, but also in judging the radicality of a surgical resection (V). The effect of surgical and radiological treatment of metastases can also be measured by changes in serotonin in blood (VI, VII). Hence, it seems as if serotonin as a marker is best used in the evaluation of different treatments, and not in screening for a carcinoid tumor.

Substance P has been demonstrated in foregut (176), midgut (7) and hindgut (199) carcinoids. In addition, an ovarian carcinoid (177) and liver metastases from an unknown primary tumor (190) have been shown to contain substance P. Plasma levels of this peptide have been studied in normal humans (175) and patients with various disorders (38, 80, 95, 139). Some reports (69, 176, 177) have shown that patients with carcinoid tumors may have elevated levels of substance P in plasma. One interesting finding was a patient with an ovarian tumor with normal values of 5-HIAA but high levels of substance P in plasma

and tumor tissue (177). In our studies (II, III) we also found patients with normal 5-HIAA and increased plasma substance P. All but one patient had high levels of substance P in plasma (III). It thus seems that substance P may be complementary to 5-HIAA in urine and serotonin in plasma as a carcinoid tumor marker and in some cases a better one.

Several other peptides with increased levels in circulating blood have been found. Pancreatic polypeptide (PP) levels are high in 50 % of cases reported (2, 213). Human chorionic gonadotropin (HCG) or its subunits has also been found in high concentrations in patients with carcinoid tumors (71, 160, 215). Other peptides are kinin (135), bradykinin (179) and growth hormone (209). In addition, histamine (134) and prostaglandins are secreted by carcinoid tumors (84, 178). Whether all of these compounds are secreted by the tumor itself is not yet known. So far no study has compared the tumor peptide content with the corresponding blood content of regulatory peptides (cf II and III).

The pancreatic endocrine tumors differ significantly from the other gastrointestinal endocrine tumors. Their characteristic clinical syndromes are correlated to plasma levels of peptides and the majority peptide population in the tumor tissue (99). In many of these cases a single plasma sample may be the only diagnostic method necessary. A refined localization of the tumor may be obtained by portal vein catheterization and analyses of samples from the pancreatic veins (157).

Radiology. According to Hudson and Margulis (77) small bowel barium examination gives typical filling defects and kinked bowel loops in a series of 12 patients with ileal carcinoids. Moertel (125), however, showed that radiographic diagnosis of these tumors was difficult because of small tumors, deep mucosal lesion, and intermittent obstruction.

Angiography of the superior mesenteric artery seems to be the best radiological diagnostic tool (27) with four signs suggesting a carcinoid tumor:

1. Stellate arterial appearance.
2. Narrowing of peripheral mesenteric branches.
3. Poor or moderate accumulation of contrast medium.
4. No filling of veins draining the growths.

In a series of 19 investigations selective mesenteric phlebography was compared to angiography in the localization of carcinoid tumor growth (156). In all cases where arterial changes were present, the phlebography more clearly showed the extent of venous occlusion than did the venous phase at arteriography. Lymph node and liver metastases, however, were better demonstrated by arteriography. The phlebography

thus does not seem to add any significant information compared to angiography. Moreover, it is a more complicated diagnostic method and it is considerably more painful for the patient.

The appearance of liver metastases from carcinoid tumors has been sparsely reported by angiography (27) as well as by computed tomography (CT) (208). In our series (IV) we can confirm previous reports on the hypervascularity of the metastases but in our study most of them (78 %) had slight to moderate neovascularity. Furthermore, we found 4 of 27 tumors to be hypovascular, and several of the metastases detected were less than 1 cm in size. A CT scan performed in 13 patients failed to demonstrate metastases in 5 cases both before and after intravenous contrast enhancement. Due to these findings angiography still seems to be the best radiological method for discovering liver metastases. Besides, it provides valuable information on the anatomy of the hepatic vascular bed and the patency of the portal vein.

To enhance diagnostic sensitivity, we have combined selective mesenteric vein catheterization with blood sampling for determination of serotonin (V). Ten patients were investigated and the results of catheterization and serotonin determination were confirmed at a subsequent operation. 5-HIAA in urine was normal in 4 patients despite carcinoid tumor growth, and the angiograms were false negative in 2 cases. The usefulness of the catheterization and sampling technique is very much dependent on an atraumatic technique, high selectivity in the catheterization and optimal handling of the samples. If these demands are fulfilled, it is a very useful procedure not only in the localization of carcinoid tumors, but also in the follow-up of patients operated on, and whenever there is a suspicion of remaining tumor growth or recurrence.

Summary of the present study. This study has shown the superiority of selective mesenteric vein catheterization and blood sampling for the determination of serotonin in the diagnosis and follow-up of carcinoid tumors. In addition, liver angiography could detect liver metastases, some less than 1 cm in size, while CT performed on the same patients failed in 40 % of the cases to detect the metastases regardless if intravenous bolus contrast was given or not. Previously have isolated cases with carcinoid tumors been reported to have elevated levels of substance P in plasma, but this study has shown, in almost all cases of midgut tumors measured, high levels of substance P in plasma. This correlates with our finding that all midgut tumors contain substance P.

We have also been able to demonstrate in the present study that the substance P-like immunoreactivity in human plasma is identical with authentic undecapeptide substance P.

Treatment

It is now widely accepted that the carcinoid is a malignant disease and should be treated as such with radical surgery of the primary tumor (117, 197). The appendiceal carcinoid is a special case where some authors prefer radical surgery because of reports on metastatic disease (23, 63, 100, 115, 194). Others recommend a more conservative approach (127, 148, 189), particularly in children (10, 163, 188). Our paper (1) supports the conservative approach of using simple appendectomy when the tumor is restricted to the appendix. None of the patients investigated died or showed signs of recurrence.

Inextirpable tumors and symptomatic metastatic disease create problems for both the patient and the doctor. The patient experiences symptoms from both the tumor mass and the liberated hormones. The doctor can use more or less extensive treatments, knowing that some patients with an advanced metastatic disease survive many years without treatment (13, 67, 76, 125).

Medical therapy. Medical therapy for symptomatic relief of the carcinoid syndrome includes antiserotonin and antikinins agents (48, 85, 168), but this treatment has not often proven effective. A few reports have shown inhibition of the carcinoid flush and diarrhea by somatostatin (39, 56, 92, 105) and by a combination of histamine H_1 and H_2 receptor antagonists (81, 82, 152). However, the somatostatin had to be administered intravenously. As long as no somatostatin analogues with long-term action are available, this drug cannot be used in the routine treatment of the carcinoid syndrome.

Many pancreatic endocrine tumors are malignant and have widespread metastatic growth making radical surgery impossible. In the case of Zollinger-Ellison syndrome symptomatic relief can be obtained by histamine H_2 blockers (28).

Chemotherapy. At least 24 different cytotoxic drugs have been used to treat the carcinoid syndrome (70), but no real success has been reported. Streptozotocin is the most known and used drug (33, 49, 128, 129, 170). It is useful in the treatment of malignant endocrine pancreatic tumors but has poor effect on gastrointestinal carcinoid tumors (213).

Radiotherapy. Irradiation of carcinoid tumors is of little value although a few reports have shown palliation and cure by radiation therapy (57, 122, 161, 195).

Surgical therapy. The best treatment for a patient with metastatic carcinoid growth is surgery. The primary tumor and as much as possible of the metastases should be resected in order to reduce the total tumor mass. When hepatic metastases are confined to one lobe a lobectomy may be performed (59, 204, 205, 210). Local enucleation has

also been used (184), but usually the metastases are numerous and scattered in both liver lobes (IV). As both primary and secondary liver tumors are chiefly supplied by blood from the hepatic artery (24, 29, 172), interruption of the arterial liver blood flow creates ischemia and necrosis of the metastases. Several methods for ischemic treatment of liver metastases have been used including hepatic artery ligation (HAL) (44, 55, 87, 94, 113, 131, 132, 183), hepatic artery dearterialization (5, 14, 22, 30, 78, 79, 91, 120, 173), and hepatic artery occlusion (45, 73). The results reported are fairly positive, but almost all reports consist of a mixture of primary diagnoses or only a few cases, making it difficult to evaluate the effect on a single diagnosis. Furthermore, the mortality and complication rates were high when dearterialization was performed. Temporary hepatic dearterialization (19) is a method with few complications and low mortality rates. It also has the advantage of no development of collateral circulation. In addition, the procedure can be repeated and the hepatic artery used for infusion chemotherapy and for angiographic controls. We have used this method in 16 patients with metastatic carcinoid tumors (VI) who experienced relief from symptoms for at least 6 months after the treatment. 5-HIAA in urine and serotonin in platelet-poor plasma also decreased after treatment, and angiographic controls showed tumor regression. Two patients died postoperatively; both had undergone small bowel resection together with the dearterialization. This may indicate that the dearterialization is a major trauma and no concomitant procedure should be performed. The surgical procedure enables an estimation of the metastatic growth and also an opportunity to collect tumor tissue for optimal histochemical and cytochemical classification (II).

Embolization. Some patients with troublesome symptoms from metastatic carcinoid tumors cannot be operated on. Previous operations might have revealed technical difficulties not permitting a temporary dearterialization or the patient might be in such bad condition that a surgical trauma would be too hazardous. In those cases we have used a percutaneous catheterization and embolization of the liver by gelatin foam powder (VII). This technique has been extensively used in the management of gastrointestinal bleeding (159) but also in variceal (107) and renal (89) bleeding. Embolization of the spleen for treatment of hypersplenism has been performed successfully (6, 114, 141), and preoperative embolization of renal carcinomas (53) is extensively used. Benign tumors can sometimes be successfully treated by embolization alone (35). Palliative embolization of inoperable malignant tumors or metastases (64) may improve quality of life and sometimes prolong survival time. Patients suffering from symptomatic malignant endocrine tumors seem to experience the greatest benefit from palliative tumor embolization (3, 26, 43, 75). In our series (VII) we treated 8 patients by gelatin foam powder embolization of the liver. The tumor mass in the liver was reduced in all patients and the carcinoid syndrome disappeared after the embolization in 5. No major adverse reactions were noticed and no "carcinoid crisis" occurred

in spite of the fact that no pretreatment was given. 5-HIAA in urine was decreased in all but one patient, while serotonin in platelet-poor plasma and whole blood did not change uniformly. In the formation of serotonin from 5-hydroxytryptophan, the aromatic amino acid decarboxylase in the tumor is used. The major part of the circulating serotonin is then converted to 5-HIAA by the enzymes monoamineoxidase (MAO) and aldehyde dehydrogenase (AD). In this process the embolization may effect the activity of different enzymes and thus change the degradation pattern. Feldman has shown that a majority of the patients with the carcinoid syndrome secrete both serotonin and 5-hydroxytryptophan in urine (50). Hence, measurement of these 2 compounds and not only 5-HIAA in urine might better reflect the biochemical changes after therapeutic treatment of metastatic carcinoid tumors.

Summary of the present study. The study of temporary liver dearterialization is the largest and most homogeneous group of patients presented. Fourteen patients were followed for at least 6 months and all but 1 were free from symptoms during this time. Two patients have had no recurrence of the carcinoid syndrome for 34 and 42 months, respectively. The results are very satisfactory and indicate that this is the treatment of choice concerning liver metastases from carcinoid tumors.

In 8 patients a liver embolization with gelatin foam powder was performed. The carcinoid syndrome disappeared in 5 patients and after 6 months 3 patients still were free from symptoms despite an advanced disease. If surgery is not possible, the liver embolization is a valuable alternative treatment.

CLINICAL IMPLICATIONS AND FUTURE ASPECTS

These studies have pointed out and elaborated upon some important clinical difficulties in the management of gastrointestinal endocrine tumors.

1. Most patients have experienced symptoms long before the diagnosis is made and, by that time, the majority already have metastases. The survival rate is dependent on the extent of metastases but there are cases with massive metastatic growth surviving many years.
2. The malignant potency of a carcinoid tumor is difficult to predict. The metastatic extent is an important feature, but other factors such as the site of origin of the primary tumor, the histological growth pattern of the tumor, and peptide and amine content in the tumor and circulating blood may contribute to the potential malignant course.
3. Modern histo- and cytochemical techniques have revealed new aspects of the carcinoid concept. It is therefore important that the handling of tumor tissue is performed under optimal conditions in order to facilitate the classification. This may have implications for future treatment and follow-up.
4. Early detection of the carcinoid tumor is important, according to survival rates. Unfortunately there are no specific diagnostic methods. Computed tomography has compared to angiography not turned out to be reliable in detecting liver metastases. Selective mesenteric vein catheterization and blood sampling for amines and peptides may be used successfully both in the localization of tumors and the analysis of substances secreted.
5. Many carcinoid tumors contain several peptides. Therefore an analysis of the corresponding plasma values may be of interest. So far no comprehensive study of this kind has been performed.
6. The only effective treatment of the carcinoid tumor and its metastases is surgery. When radical resection is impossible a reduction of the tumor mass may abolish or reduce the clinical symptoms. The metastatic carcinoid may successfully be treated by temporary hepatic dearterialization and in cases of advanced disease not permitting surgery, percutaneous hepatic embolization may be performed.
7. The diagnosis, classification and treatment of the carcinoid tumor are aspects in a great transformation. Due to this and the rarity of the tumor, national or even international cooperation is warranted in order to obtain reliable results in a reasonable time period.

GENERAL SUMMARY

This thesis comprises studies on the classification, diagnosis and treatment of gastrointestinal endocrine tumors with special reference to midgut tumors.

In a retrospective study 156 patients with carcinoid tumors were analyzed with respect to different clinical parameters. These were correlated to the extent, size and site of the tumors. In order to refine the classification of carcinoids, tumors of foregut, midgut and hindgut origin were investigated by immunocytochemistry, histochemistry and growth patterns. The radiological appearance of liver metastases on angiography and computed tomography was evaluated in 27 and 13 patients, respectively. The combination of mesenteric vein catheterization and blood sampling for determination of amines and peptides was performed in 10 patients, and in another study the substance P levels were measured in blood from the hepatic vein and a peripheral vein in 10 patients with known liver metastases from carcinoid tumors. The general treatment of carcinoid tumors was discussed in the retrospective study and the handling of liver metastases was illustrated with temporary liver dearterialization and gelatin foam embolization of the liver. From these studies the following general conclusions can be drawn:

1. Most carcinoid tumors are asymptomatic or have no specific symptoms, resulting in a high incidence of metastases at the time of diagnosis.
2. The survival rate is clearly correlated to the size of the primary tumor and the extent of metastases.
3. The midgut endocrine tumors have been shown to be homogeneous, generally containing serotonin and substance P in the tumor cells.
4. Patients with midgut tumors have substance P not only in the tumor but also in circulating blood. Patients with liver metastases and normal values of 5-HIAA in urine may have high levels of substance P in plasma suggesting that this substance may be a useful carcinoid tumor marker.
5. Detection of liver metastases and metastatic extent is best made by analysis of serotonin after selective mesenteric vein catheterization and blood sampling. Computed tomography is not useful in the diagnosis of liver metastases.
6. Treatment of carcinoid tumors is primarily surgical. When radical surgery is not possible, reduction of tumor mass may be beneficial and palliative treatment of liver metastases may be performed with good results by temporary liver dearterialization. Patients not possible for a laparotomy may be treated by percutaneous hepatic embolization.

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I've done it, I've done it!
Guess what I have done!
Invented a light that plugs into the sun.
The sun is bright enough,
The bulb is strong enough,
But, oh, there's only one thing wrong ...

The cord ain't long enough.

Shel Silverstein

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CARCINOID TUMORS IN THE GASTROINTESTINAL TRACT—AN ANALYSIS OF 156 CASES

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Abstract. A series of 156 patients with gastrointestinal carcinoid tumors is presented. The tumors were grouped as foregut, midgut and hindgut carcinoids. The appendiceal tumors were grouped separately. Lack of specific symptoms resulted in only 26% correct presumptive diagnoses. This also reflected the patient's delay >2 years in 10% and doctor's delay >2 years in 29%. In the larger group (midgut), 41% were multiple primary tumors. Liver metastases were found in 46% and tumors bigger than 1 cm metastasized to the liver in 58%. The five-year survival of patients with liver metastases was 43% while the figure for those without metastases was 80%. In 47 patients with appendiceal carcinoids, 68% had tumors <1 cm. No metastases to the regional lymph nodes, viscera or skeleton were found. Thirty-three patients were traced and none had died of the tumor. Two foregut and 4 hindgut tumors were re-examined using immunocytochemistry. In one of the foregut tumors, cells containing serotonin were found while the other one contained gastrin cells. In 3 hindgut tumors PP-cells were seen and one of them also harbored glucagon/glicentin cells. In one hindgut tumor no peptides were found.

The term carcinoid defined by Oberndorfer (1907) is a fairly common tumor in the gastrointestinal tract. It was found in 1.2% of 16294 autopsies in a Swedish necropsy series (Berge & Linell, 1976). The tumor was first described in 1888 by Lubarsch but it was not until 1954 (Thorson, Björck, Björkman & Waldenström, 1954) that the endocrine properties of the tumor were recognized. The carcinoids have turned out to be a heterogeneous group of tumors, however, Williams & Sandler (1963) proposed that carcinoids arising in the foregut, midgut and hindgut form three distinct groups based on histological, biochemical and clinical data. This concept helps to explain the differences between carcinoids in the bronchi, stomach, duodenum, biliary system and pancreas (foregut origin), the distal small intestine, appendix, and proximal colon (midgut origin), and finally the distal colon,

and rectum (hindgut origin). The clinical relevance of this subdivision, however, has to be further evaluated. The carcinoid was initially regarded as a carcinoma without malignant attributes (Oberndorfer, 1907), but it is now obvious that most carcinoids outside the appendix metastasize with time and that the median survival time in patients with liver metastases is only two to three years (Moertel & Hanley, 1979). Carcinoids therefore constitute an important group of neoplasms deserving careful assessment and discerning management.

In this paper we present data on 156 patients with carcinoid tumors diagnosed over a 35-year period. In addition the tumor specimens available from foregut and hindgut tumors were investigated for their peptide content by immunocytochemistry.

MATERIAL AND METHODS

The case history records of 156 patients with gastrointestinal carcinoid tumors were analyzed retrospectively. One hundred and twenty-one of these records were from patients treated at the Surgical and Gynecological Departments in Lund between 1945-1979 (clinical patients) and 35 were records from patients with tumors diagnosed at autopsy between 1952-1979 (autopsy patients). The analysis comprised of patient age, symptoms, clinical features, clinical diagnosis, patient's and doctor's delay, tumor size, multicentricity, tumor distribution, metastases, additional primary neoplasms of other types and survival. The histopathological diagnosis was based on sections routinely stained with hematoxylin and eosin. Most specimens were also stained with silver according to Masson (argentaffin staining). Specimens of foregut and hindgut tumors well preserved as judged by examination of hematoxylin-eosin-stained sections and specified in Tables IV and XIII were re-examined using immunocytochemistry for the demonstration of neurohormonal peptides (for details on the immunocytochemical procedures and antisera see Alumets, Alm, Falkmer, Håkansson, Ljungberg, Mårtensson, Sundler & Tibblin, 1981; Alumets, Sundler, Falkmer, Håkansson, Ljungberg, Lassi, Mårtensson &

Table I. Distribution and method of discovery of 156 carcinoid tumors

Location	Clinical patients	Autopsy patients	Total
Stomach	4	—	4
Duodenum	2	2	4
Jejunum	1	4	5
Meckel	3	—	3
Ileum	57	23	80
Appendix	45	2	47
Colon	1	3	4
Rectum	8	—	8
Unknown	—	1	1
Total	121	35	156

Nobin, 1983) and using the Falck-Hillarp histofluorescence technique (Falck, 1962; Falck, Hillarp, Thieme & Torp, 1962; Björklund, Falck & Owman, 1972) for the demonstration of intracellular amines. Midgut tumors were not analyzed immunocytochemically since substance P, the predominating peptide in such tumors (Nobin et al., 1982; Mårtensson et al., 1983) cannot be demonstrated unequivocally in specimens routinely processed for histopathology (Alumets et al., 1983). The carcinoids were grouped according to their location as foregut carcinoids (stomach, duodenum and pancreas), midgut carcinoids (jejunum, ileum and proximal colon) and hindgut carcinoids (distal colon and rectum). The appendiceal carcinoids were grouped separately. Data such as tumor size, multicentricity, and occurrence of metastases were obtained from the description by the surgeon or the pathologist. The primary tumor size, measured before fixation, was categorized under one of the headings: <1 cm, 1–2 cm, >2 cm. Patient's and doctor's delays were calculated from individual records. Recently we tried to contact the 121 clinical patients and succeeded in tracing 109. Of this group 70 were alive and were subjected to a clinical examination. The cause of death was checked for the other 39 patients. The 12 patients who were not traced all had appendiceal carcinoids. From these data the survival

Table II. Age at diagnosis of 156 carcinoid tumors

Clinical patients	
Excluding appendix (76 patients)	
Mean	58.2
Median	58
Range	28–81
Appendix (45 patients)	
Mean	34.6
Median	31
Range	9–84
Autopsy patients (35 patients)	
Mean	70.8
Median	72
Range	44–88

Table III. Associated primary neoplasms in 76 clinical and 33 autopsy patients with carcinoid tumors in the gastrointestinal tract excluding appendix

	Autopsy patients	Clinical patients	Total
Neurinoma	1	—	1
Pulmonary cancer	2	—	2
Acute leucemia	1	—	1
Pancreatic cancer	1	—	1
Colonic cancer	2	1	3
Fibrosarcoma	1	—	1
Hepatoma	1	—	1
Breast cancer	1	—	1
Hyperparathyroidism	1	2	3
Rectal cancer	1	—	1
Prostatic cancer	—	1	1
Gastric cancer	—	2	2
Malignant lymphoma	—	1	1
Gastrinoma	—	1	1
Renal cancer	—	1	1
Lymphosarcoma	—	1	1
Malignant melanoma	—	1	1
Total	12	11	23

was calculated. The crude survival rate with no correction was compared to the survival when hospital mortality and death for other reasons were excluded.

RESULTS

General observations. The location and method of discovery of the 156 carcinoid tumors are presented in Table I. Eight carcinoids were of foregut origin, 138 of midgut origin and nine of hindgut origin. The average age of the clinical patients at time of diagnosis of extra-appendiceal carcinoids was 58 years, while carcinoids in the appendix generally were diagnosed at a younger age. The autopsy patients were on average more than 70 years old (Table II). The frequency by which extra-appendiceal carcinoids were found to co-exist with other primary neoplasms was 14% in the clinical cases and 36% in the autopsy cases (Table III).

Foregut carcinoids. Data pertaining to eight patients with foregut carcinoids are presented in Table IV. Symptoms referable to the carcinoid tumor *per se* were present in three patients (no. 4, 5 and 6), while the carcinoids were *en passant* findings during investigation or treatment for other diseases in three patients (no. 1, 2 and 3) and were found at autopsy in two patients (no. 7 and 8). The urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA)

Table IV. Foregut carcinoids. Patient and tumor data from eight cases

Case Age Sex	Tumor manifestation	5-HIAA/ urine	Humoral manifestations		Tumor peptides ^a and amines	Clinical features	Treatment	Comments
			Sero- tonin	Other				
1 63 M	2 polyps in the stomach (corpus). No metastases	Normal	Normal	Gastrin	Not tested	Epi- gastric pains	Excision	Well 3 years postoperatively
2 77 M	1 polyp in the stomach (corpus). No metastases	Not re- corded	Normal	Not re- corded	Not tested	Gastric cancer	Total gastrec- tomy	Gastric cancer and carcinoid polyp. Died 1 year postoperatively
3 36 F	1 tumor in the stomach (corpus). Liver and lymph node metastases	Moder- ate eleva- tion	Normal	Cortisol ACTH	Sero- tonin	Hepa- tomegaly and ascites. Pigmen- tation	Excision of gastric tumor and liver em- bolization	Died 5 months post- operatively
4 64 F	1 tumor in the duodenum. No metastases	Normal	Not re- corded	Not re- corded	Not tested	Bleeding gastric ulcer	B II resection	En passant finding. Died 7 years post- operatively in heart failure
5 41 M	1 polyp in the duodenum	Not re- corded	Not re- corded	Gastrin	Gastrin	Recurrent duodenal ulcer	Excision	14 years postopera- tively total gastrec- tomy and pancreatic resection because of Z-E. HPT-operation. No signs of carcinoid 19 years after the first operation
6 66 M	Bronchial ade- noma. Duodenal carcinoid with metastases in liver, spleen, spine and lymph nodes	Moder- ate eleva- tion	Normal	Not re- corded	Not tested	Silent bronchial tumor. 5 years later carcinoid syndrome	Lobar resection of the lung. Enucleation of meta- stases and temporary liver dear- terialization	Died 9 years after the pulmonary operation
7 84 M	Duodenal tumor. No metastases	Not re- corded	Not re- corded	Not re- corded	Not tested	None	None	Autopsy finding
8 80 M	Duodenal tumor. Lymph node me- tastases	Not re- corded	Not re- corded	Not re- corded	Not tested	None	None	Autopsy finding

^a Data from Alumets et al. (1983).

was determined in four patients and was found to be slightly elevated in two. Blood serotonin was normal in the four patients measured. In two patients (no. 1 and 5) serum gastrin levels were high. One of these (no. 5) had the Zollinger-Ellison syndrome. In one patient (no. 3) cortisol and ACTH levels in plasma were elevated and the patient also developed symptoms of Cushing's disease. No patients with a gastric carcinoid had pernicious anemia or achylia. Two tumors were re-examined mi-

croscopically. In one (no. 3) serotonin-containing cells were found (Fig. 1a). The gastrinoma (no. 5) contained gastrin cells as the majority cell population whereas no peptide was detectable in the tumor from patient 4. Two of the patients (no. 3 and 6) had carcinoids with distinct malignant characteristics, and they died of the disease. Of the other clinical patients two died of other causes and two are alive (Table IV).

Midgut carcinoids (excluding appendiceal car-

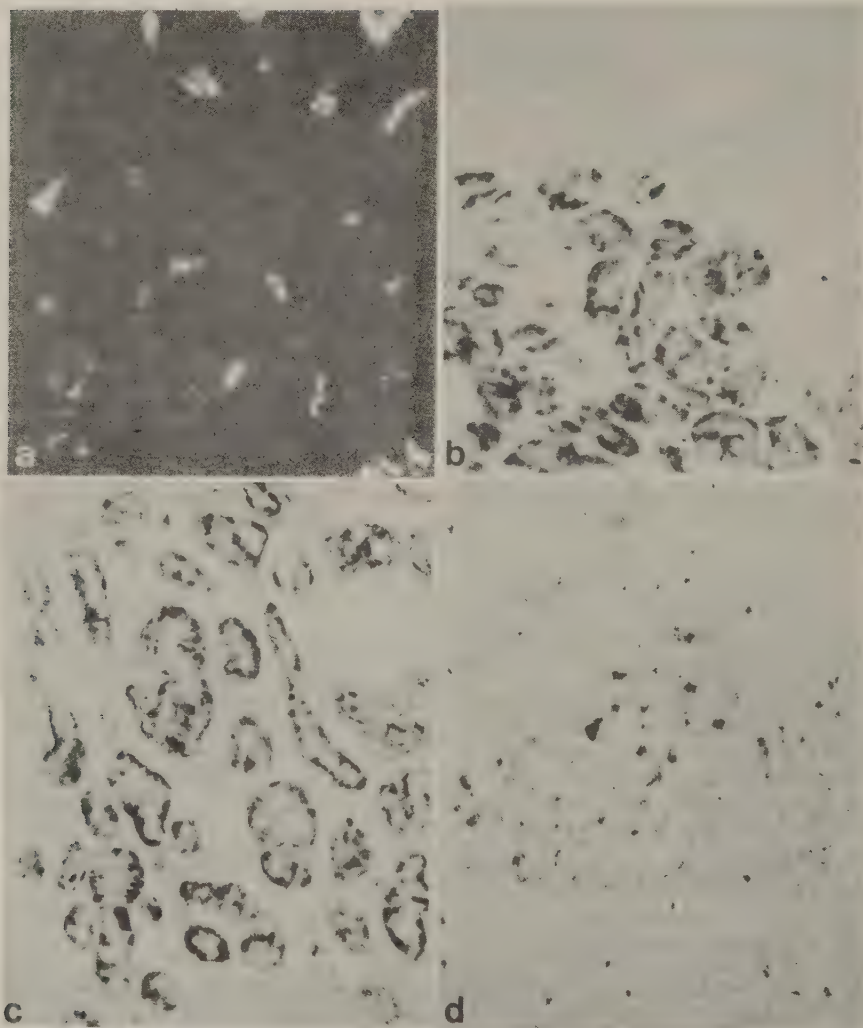


Fig. 1. (a) Foregut tumor, case 4. Gastric carcinoid. Scattered cells display yellow formaldehyde-induced fluorescence due to their content of 5-HT ($\times 200$). (b) Hindgut tumor, case 6. Rectal carcinoid. Section immunostained for PP. Virtually all tumor cells contain immunoreactive PP. Mucosa at top of figure ($\times 150$). (c) and (d) Hindgut

tumor, case 2. Rectal carcinoid. Sections immunostained for glucagon (c) and PP (d). The majority of tumor cells contain immunoreactive glucagon, whereas the PP immunoreactive cells constitute a minority cell population in this tumor ($\times 150$).

Table V. Age at diagnosis in 91 patients with midgut carcinoids

Age	Clinical	Autopsy	Total
21-30	1	—	1
31-40	5	—	5
41-50	8	5	13
51-60	18	1	19
61-70	17	7	24
71-	12	17	29
Total	61	30	91

Table VII. Patient's and doctor's delay in 61 clinical patients with midgut carcinoids

Delay (years)	Patient's	Doctor's
-0.5	43	26
0.5-1	7	4
1-2	1	12
2-	6	17
Not judgable	4	2
Total	61	61

cinoids). In 91 patients the tumor was of midgut origin, with five tumors originating in the jejunum, three in Meckel's diverticula, 80 in the ileum and three in the caecum. Age at the time of diagnosis ranged in the clinical series from 30 to 81 years, with a median age of 56 years. In the autopsy series the range was 44 to 88 years, with a median age of 72 (Table V). Thirty-six per cent of the patients experienced symptoms associated with the carcinoid tumor for more than two years before correct diagnosis was made, and 25% had symptoms for more than four years (Table VI). Patient's delay was more than two years in 10%, while a doctor's delay of more than two years occurred in 29% (Table VII). The main clinical symptoms at the time of diagnosis were abdominal pains, diarrhoea, flush or intestinal obstruction (Table VIII). A presumed correct diagnosis of carcinoid occurred in only 26% of the cases; the remaining 46 patients had 17 different diagnoses (Table IX). Some of these diagnoses were based on symptoms of coinciding disease. The carcinoid tumors in these cases usually gave no specific symptoms and were en passant findings. An example was a patient presenting with a groin hernia which was an incarcerated Littre's hernia with the carcinoid in the Meckel's diverticulum. A

solitary primary carcinoid tumor was observed in 52 patients whereas 37 patients had multiple tumors, a finding which underlines the importance of being aware of the multiplicity of carcinoids. It was more common for primary tumors to be solitary with increasing tumor size (Table X). Liver metastases were recorded in 46% of the patients, and there seemed to be a correlation between primary tumor size and the frequency of metastases. Thus, tumors smaller than one centimeter in diameter metastasized to the liver in 22% of the patients while tumors bigger than one centimeter metastasized in 58% (Table X). A five-year survival was possible in 34 patients; another 27 have been diagnosed during the last five years of this study. If no correction for hospital mortality and death by other causes was made, the average five-year survival was 53% and the five-year survival in patients with liver metastases was 43%. When no metastases were present the survival was 80% (Table XI). Among the 27 patients diagnosed during the last five years, those without metastases are all alive, while seven of 18 patients with liver metastases have died (Table XII).

Hindgut carcinoids. The nine patients with hindgut carcinoids are presented in Table XIII. One

Table VI. Duration of symptoms before diagnosis in 61 patients with midgut carcinoids

Years	Total
-1	28
1-2	11
2-4	7
4-10	8
10-	7
Total	61

Table VIII. Main clinical symptom in 61 patients with midgut carcinoids diagnosed in life

Symptoms	No.
Abdominal pain	16
Diarrhea	16
Flush	10
Melena	4
Intestinal obstruction	13
Ascites	2
Total	61

Table IX. Clinical diagnosis in 61 patients with midgut carcinoid tumors at time of carcinoid diagnosis

Diagnosis	No.
Metastatic adenocarcinoma	1
Peritonitis	1
Groin hernia	1
Appendicitis	8
Carcinoid	16
Cholecystitis	5
Intestinal obstruction	13
Colonic cancer	4
Lymphosarcoma	1
Crohn's disease	2
Duodenal ulcer	1
Acute abdomen	1
Pancreatic cancer	1
Tumor in small intestine	2
Abdominal tumor	1
Liver cirrhosis + esophageal varices	1
Diaphragmatic hernia	1
Neurofibroma Recklinghausen	1
Total	61

tumor was of sigmoid origin and eight were of rectal origin. The rectal tumors were discovered during investigation for rectal bleeding (three patients), constipation (two patients), bowel discomfort (two patients) and prostatism (one patient). The sigmoid tumor was manifested with hepatomegaly due to metastases. In four patients 5-HIAA in urine was measured and found to be elevated only in one patient (no. 7) who had a large rectal tumor with liver metastases. The patient with sigmoid tumor (no. 1) accompanied by liver metastases had normal excretion of 5-HIAA in urine. Specimens of four tumors were analyzed immunocytochemically. Three tumors (no. 2, 4 and 6) harbored PP-immunoreactive cells (Fig. 1 *b* and *d*) and one (no. 2) in addition contained glucagon/glicentin cells (Fig. 1 *c*). In one (no. 7) no peptides were detectable. Three patients died due to the carcinoid tumor.

Two of them had liver metastases at the time of diagnosis and one had multiple rectal tumors. One patient died of a bleeding gastric ulcer. Five patients are alive 1–16 years after the diagnosis was established.

Appendiceal carcinoids. In 47 patients a carcinoid tumor in the appendix was found, 45 at operation and two at autopsy. Among the operated patients 28 had suspected appendicitis and in 17 (15 women and two men) appendectomy was performed en passant. The tumor size and extent of metastases are shown in Table XIV. No one had metastases in the regional lymph nodes or more distantly. Simple appendectomy was performed in 39 patients and bowel resection in six patients (one hemicolectomy, four ileocaecal resections, one caecal resection). The bowel resections were decided upon because of tumor growth in the entire appendix or growth into the base. Of the 45 clinical patients 33 have been traced and examined. None have died of the tumor and there are no signs of metastases or tumor recurrence to date.

DISCUSSION

The histopathological definition of "carcinoid" was introduced by Oberndorfer (1907), and Masson (1928) proposed the term "argentaffin cell tumor". During the last decades new aspects of the carcinoid entity were discovered such as the endocrine nature, and the specific histochemical properties of the tumor cells (Jacobson, 1954; Lembeck, 1954; Sandler & Snow, 1958). Therefore Williams & Sandler (1963) suggested a classification based on the embryologic site of origin into foregut, midgut and hindgut tumors. During the last 15 years new information about origin (Pearse, 1969) and ultrastructure (Solcia et al., 1978) of the tumors and their content of peptides and amines (Alumets et al., 1983) has made the concept more complex. A num-

Table X. Tumor size, multicentricity and metastases in 91 patients with midgut carcinoids diagnosed in life and at autopsy

Size	Total	Solitary	Multiple	Not recorded	No metastases	Lymph node metastases	Liver metastases
<1 cm	32	16	16	—	18	7	7
1–2 cm	30	18	12	—	6	7	17
>2 cm	20	14	6	—	—	8	12
Not recorded	9	4	3	2	1	2	6

Table XI. Five-year survival of patients with midgut carcinoids

Stage	No. of patients	5-year survival	%
No metastases	5 (4)	4 (4)	80 (100)
Lymph nodes	6 (5)	4 (4)	67 (80)
Liver metastases	23 (18)	10 (10)	43 (56)
Total	34 (27)	18 (18)	53 (67)

Figures in () represent numbers when hospital mortality and death by other causes are excluded.

Table XII. Survival of patients with midgut carcinoids followed less than five years

Stage	No. of patients	No. of patients living	%
No metastases	3 (3)	3 (3)	100 (100)
Lymph nodes	6 (6)	6 (6)	100 (100)
Liver metastases	18 (16)	11 (11)	61 (69)
Total	27 (25)	20 (20)	74 (80)

Figures in () represent numbers when hospital mortality and death by other causes are excluded.

ber of studies during the last decade using histochemical techniques for the demonstration of amines and neurohormonal peptides have revealed that gastrointestinal carcinoids are extremely heterogeneous with respect to their content of sero-

tonin and bioactive peptides. Thus, whereas most foregut and hindgut tumors lack serotonin-containing cells, such cells as a rule predominate in midgut tumors. The spectrum of different neurohormonal peptides also differs between carcinoids aris-

Table XIII. Hindgut carcinoids. Patient and tumor data from nine cases

Case Age Sex	Tumor manifestation	5-HIAA/ urine	Tumor peptides*	Clinical features	Treatment	Comments
1 68 F	Sigmoid tumor. Liver and lymph node metastases	Normal	Not re- corded	Liver enlargement		Died during the investiga- tion of liver enlargement
2 55 M	Rectal tumor. No metastases	Not re- corded	Glucagon/ glicentin PP	Rectal bleeding	Excision	No recurrence one year later
3 44 F	Rectal tumor. No metastases	Not re- corded	Not re- corded	Rectal bleeding	Excision	No recurrence 16 years later
4 44 M	Rectal tumor. No metastases	Not re- corded	PP	Obstipation	Excision	No recurrence 11.5 years later
5 28 M	Rectal tumor. No metastases	Not re- corded	Not re- corded	Rectal bleeding	Excision	No recurrence 10.5 years later
6 55 F	Rectal tumor. No metastases	Normal	PP	Bowel discomfort	Excision	No recurrence 3.5 years later
7 64 M	Big rectal tumor. Liver metastases	High	No pep- tides de- tectable	Obstipation	Excision and liver dearteri- alization	Died 1.5 months after the operation
8 72 M	Multiple rectal tumors	Normal	Not re- corded	Bowel discomfort	Excision	Died 4.5 years later with sign of liver metastases
9 69 M	Rectal tumor. No metastases	Not re- corded	Not re- corded	Prostatism	Excision	14 years later, renal cancer. Death in one year because of bleeding gastric ulcer. At autopsy no metastases

* Data from Alumets et al. (1981).

Table XIV. *Metastases related to tumor size in 47 appendiceal carcinoids*

Size	No metastases	Local metastases
<1 cm	32	1 (mesoappendix)
1-2 cm	11	-
>2 cm	-	-
Whole appendix	3	-
Total	46	1

ing within foregut, midgut and hindgut. Thus, both foregut and hindgut tumors often contain a variety of peptides such as gastrin, somatostatin, PP and glucagon, whereas midgut tumors seem to contain substance P only.

The present and previous studies (Friesen, Hermreck & Mantz, 1974; Larsson et al., 1975; Alumets et al., 1981, 1983; O'Brian et al., 1982; Emson et al., 1982; Larsson et al., 1982; Mårtensson et al. 1983) have shown that carcinoid tumors can produce more than one hormone, and it has also been suggested that one tumor cell may produce more than one hormone (Sundler et al., 1979). Furthermore, the hormones produced by the majority cell population do not necessarily give rise to the clinical symptoms, and the majority cell population in the metastasis may sometimes differ from that of the primary tumor (Friesen et al., 1974). The histogenesis of carcinoids has been suggested to be a neoplastic transformation of multipotent endocrine stem cells sometimes differentiating into multiple endocrine cell lines (Soga, 1976; Larsson, 1979; Alumets et al., 1982). From a clinical point of view we have found the classification into foregut, midgut and hindgut tumors practical and convenient since those groups of tumor differ with respect to the serotonin content and to the spectrum of neurohormonal peptides (see also Alumets et al., 1981, 1983; O'Brian et al., 1982; Larsson et al., 1982; Mårtensson et al., 1983). An important problem in the diagnosis of many carcinoid tumors is the lack of specific symptoms (Table VIII) and the lack of reliable routine laboratory tests. This is reflected in the patient's and doctor's delay in diagnosing the tumor as is also shown by Moertel et al. (1961). Among laboratory diagnostic techniques determination of 5-HIAA in urine is the one most commonly used. This serotonin metabolite has been claimed to be a marker not only for metastatic growth but

also for the primary tumor (Dilawari & Douglass, 1979). It must, however, be emphasized that a patient may have a wide spread disease without an increase of 5-HIAA in urine. This is particularly evident concerning foregut and hindgut tumors (Thompson, Gee & Little, 1979) and the present study supports this view. Roentgenological examination of the small bowel and colon usually does not contribute to the correct diagnosis (Moertel et al., 1961). Angiography, however, can be useful in making the diagnosis (Boijesen, Kaude & Tylén, 1975; Sako, Lunderquist, Owman, Mårtensson & Nobin, 1982). Venous catheterization and blood sampling for the determination of neurohormonal peptides and amines is another tool in the search for a carcinoid tumor (Reichardt et al., 1979; Nobin et al., 1982, 1983). This technique cannot only provide the diagnosis but also give the exact localization and extent of the tumor. This is exemplified by our recent series of midgut carcinoids where serotonin and substance P were used as markers (Emson et al., 1982; Nobin et al., 1982, 1983). Endoscopy seems also to be a valuable tool for the diagnosis of carcinoids in the upper and lower gastrointestinal tract. Carcinoids have a distinct malignant potential (Moertel et al., 1961) and it is therefore important to treat them aggressively. Nobody argues against surgery of the primary tumor, but this should also include radical metastatic lymph node surgery. Hepatic metastases are usually accompanied by signs of a hormonally functioning tumor with great discomfort for the patient. Liver surgery with the aim of tumor reduction is therefore desirable. When the metastases are restricted to one lobe, liver resection has been reported with good results (Wilson 1959; Zeegen, Rothwell-Jackson & Sandler, 1969; Gillett & Smith, 1974). Enucleation can be used when there is a single or few metastases (Stephen & Graham-Smith, 1972). The metastases are, however, usually distributed in both lobes (Sako et al., 1982) and are often not suitable for resection or enucleation. Ischemic treatment of liver metastases has been performed in several different ways (Bengmark et al., 1974, 1982; Allison et al., 1977; Lunderquist et al., 1982; Nobin et al., 1983 b) with good effect on symptoms. We have seen excellent palliative results in a series of 16 patients with metastatic carcinoid disease treated with temporary hepatic dearterialization (Bengmark et al., 1982). When the temporary hepatic dearterialization procedure is not suitable we have

obtained good results on tumor reduction and relief of symptoms with gelfoam powder embolization of the hepatic arterial tree (Lunderquist et al., 1982; Mårtensson et al., 1983 b). These results agree with findings of Allison et al. (1977) and Blumgart & Allison (1982). The appendiceal carcinoid tumor constitutes a special problem with respect to the extent of resection giving the most optimal result. Some reports have shown very high survival rates after simple appendectomy (Moertel et al., 1968; Rydén et al., 1975), even though others (Markgraf & Dunn, 1964; Syracuse et al., 1979) have shown metastases, carcinoid syndrome and recurrence. In the present series of patients appendectomy seemed to be the proper treatment in all cases where tumor growth was restricted to the appendix. If, however, there is a growth into the caecum or lymph nodes the operation should be extended into a right hemicolectomy.

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ENDOCRINE TUMORS OF THE ILEUM - CYTOCHEMICAL AND CLINICAL ASPECTS

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ABSTRACT

Sixteen patients with endocrine ileal tumors and liver metastases were analyzed regarding primary tumor size, multicentricity, carcinoid syndrome, biochemical parameters such as serotonin and substance P in blood, and 5-HIAA in urine. In addition, tumor specimens from all patients were immediately after surgery processed for immunocytochemistry. The histological growth pattern of the tumors was classified as undifferentiated, insular, acinar, trabecular or mixed. In all patients the serotonin levels were high and 5-HIAA in urine was elevated in all but 3. Substance P in plasma was elevated in all but 1 patient measured. By immunocytochemistry serotonin cells were found in all tumors, substance P immunoreactivity in all but 1 tumor and enkephalin immunoreactivity in 1 tumor that also stored substance P. The growth pattern did not relate to survival rate, but differences between primary tumor and metastases in the same patient were noticed.

INTRODUCTION

Recent observations have indicated a characteristic spectrum of neurohormonal peptides and amines in endocrine tumors arising in foregut, midgut and hindgut derivatives, respectively. Furthermore, a correlation between hormone content in the tumors and symptoms of the patients has been found. Foregut (including pancreatic) endocrine tumors contain a wide range of neurohormonal peptides such as gastrin, insulin, glucagon, somatostatin, pancreatic polypeptide, VIP, ACTH/MSH, calcitonin and neurotensin (for references see 1). Many of these tumor peptides give rise to specific endocrine symptoms. Such symptoms were observed in about 50 % of the patients reported in recent series (1, 2). Hindgut endocrine tumors rarely cause endocrine symptoms. Nevertheless, they contain several neurohormonal peptides such as pancreatic polypeptide, glucagon, somatostatin, substance P, enkephalin, β -endorphin and insulin (3).

Many patients with midgut endocrine tumors develop a specific constellation of symptoms referred to as the carcinoid syndrome. As a rule the symptoms arise only after metastases have developed in the liver. There are preliminary reports on the occurrence of substance P in a majority cell population in midgut tumors (4, 5, 6, 7, 8, 9). In addition, there have been reports claiming the existence in such tumors also of immunoreactive somatostatin and glucagon all of them occurring in minority cell populations (7, 10, 11, 12, 13).

We have in the present study analyzed 16 midgut endocrine tumors that immediately after surgery were handled in such a way as to optimize the application of immunocytochemistry for peptides and for histochemistry of monoamines. The present study deals with the morphological and cytochemical findings obtained as well as the biochemical and clinical data recorded from the patients.

MATERIAL AND METHODS

Sixteen patients with endocrine ileal tumors and liver metastases were analyzed for primary tumor size, multicentricity, carcinoid syndrome, 5-HIAA in urine, serotonin in platelet-poor plasma (PPP) and whole blood, substance P in plasma and for follow-up.

Histochemistry

Tissue-processing. Specimens of tumor tissue were frozen immediately after surgery in a mixture of propane and propylene, cooled to the temperature of liquid nitrogen and freeze-dried. They were then fixed by exposure to vaporous formaldehyde according to the procedure described by Falck and Hillarp (14, 15, 16) or diethylpyrocarbonate (DETC) (17). All specimens were embedded in paraffin in vacuo.

Sections were cut at 6 μm . Alternatively specimens were immersed for 24 h in ice-cold formaldehyde solution (4 % in 0.1 mol phosphate buffer, pH 7.2). After thorough rinsing in buffer containing 5-10 % sucrose, the specimens were frozen on dry ice and sectioned at 15 μm in a cryostat at -20°C .

Immunocytochemistry. Paraffin sections and cryostat sections were processed for the immunocytochemical demonstration of a variety of neurohormonal peptides using the indirect immunofluorescence method of Coons et al (18) or the peroxidase anti-peroxidase technique of Sternberger (19). Antisera against the following peptides were used: substance P, enkephalin, secretin, gastrin, CCK, VIP, GIP, neurotensin, bombesin/GRP, somatostatin, glucagon, glicentin, pancreatic polypeptide, ACTH and motilin (for details on antisera see Table I). Sections incubated with antiserum preabsorbed with antigen (10-100 μg of synthetic or pure natural peptides per ml diluted antiserum) served as controls.

Growth pattern

The growth pattern of the tumors was analyzed either in the light microscope using haematoxylin and eosin stained sections, or in the fluorescence microscope using sections from formaldehyde vapor-fixed material. The growth pattern was classified by the following categories: undifferentiated, insular, acinar, trabecular and mixed (20).

Biochemistry

Serotonin determinations in platelet-poor plasma (PPP) and whole blood were performed with a HPLC technique with electrochemical detection (21). 5-HIAA in urine was measured by a spectrophotometric method (22). Substance P in plasma was determined by radioimmunoassay (23).

RESULTS

Clinical data on the patients at the time of operation and the results of the follow-up are presented in Table II. The patients comprised 9 men and 7 women with 9 solitary and 7 multiple primary tumors. Two of the primary tumors were less than 1 cm in diameter. Six tumors were 1-2 cm and 5 were more than 2 cm. In 3 tumors the size was not recorded. All patients with a primary tumor exceeding 2 cm in diameter suffered from the carcinoid syndrome while only 5 of the remaining patients had a clear-cut syndrome. The concentration of serotonin in PPP or in whole blood as well as the level of substance P in plasma were increased in all cases measured. On the other hand, a normal excretion of 5-HIAA in urine was measured in 3 patients in spite of the existence of liver metastases and in one of these patients, also of an overt carcinoid syndrome. At present 7 of the patients are dead and they all died within 2 years of the operation. Five patients are free from subjective symptoms, while 4 have regained either diarrhea or flushing or both.

Table 1. Details of the antisera

Antigen	Code	Raised against	Directed against	Working dilution	Source	References		
				Immuno- fluoresc	PAP stain- ing			
1	ACTH 1-24	No 15	protein-conj ACTH 1-24	ACTH 18-24	-	1:640	Tj B Wimersma Greidanus, Utrecht, The Netherlands	Sundler et al, 1982
2	CKK-33	"N-CKK"	protein-conj porcine CKK 1-33	N-terminus	1:10	1:640	W Schlegel, Ulm, FRG	Schlegel and Raptis, 1977
3a	Met-enkephalin	met-enk	protein-conj met-enkephalin	-	1:80	1:640	RJ Miller and KJ Chang, Burroughs Wellcome Res Lab, USA	Alumets et al,
3b	Leu-enkephalin	leu-enk	protein-conj leu-enkephalin	-	1:80	1:240	"	"
4	Gastrin 2-17	4562	protein-conj human gastrin 2-17	C-terminal tetra- peptide	-	1:5120	JF Rehfeld, Aarhus, Denmark	Lorén et al, 1979
5	GIP	ED11/19/77	unconj pure por- cine GIP	-	1:80	1:2560	T O'Dorisio, Columbus, Ohio, USA	O'Dorisio et al, 1975
6	Glicentin	R-4804	protein-conj porcine glicentin 46-69	glicentin 62-69	-	1:2560	N Yanaihara, Shizuoka, Japan	Yanaihara, 1981
7	Glucagon	7811	unconj porcine glucagon	mid portion	-	1:640	Milab, Malmö, Sweden	
8	Motilin	MBR-01	synth porcine motilin	C-terminus	-	1:640	N Yanaihara, Shizuoka, Japan	Yanaihara et al, 1978
9	Neurotensin	NC-8	protein-conj synth bovine neurotensin	C-terminal hexa- peptide	1:40	1:640	R Carraway, Boston, Mass, USA	Carraway and Leeman, 1976
10	Pancreatic polypeptide	BPP HPP	unconj bovine PP unconj human PP	-	-	1:2560 1:5120	- RE Chance, Eli Lilly, Indiana, USA	- Larsson et al, 1976
11	Secretin	5585	protein-conj por- cine secretin	-	1:80	1:2560	J Fahrenkrug and OB Schaffalitzky de Muckadell, Copenhagen, Denmark	Larsson, 1977
12	Somatostatin	19578	protein-conj somatostatin	-	-	1:2560	MP Dubois, Nouzilly, France	Dubois, 1972
13	Substance P	SP 8	protein-conj substance P	C-terminus	-	1:320	PC Emson, Cambridge, England	Brodin et al. 1981
14	VIP	7852	unconj VIP	-	1:160	1:5120	Milab, Malmö, Sweden	Alm et al, 1980

Comments

- 1 The immunostaining of the pituitary ACTH cells is blocked by ACTH 1-24, ACTH 1-39 and ACTH 7-38.
- 2 This antiserum is probably directed against the N-terminal part of CKK-33 since it does not cross react with gastrin or CKK 8.
- 3a This antiserum cross reacts with leu-enkephalin.
- 3b This antiserum cross reacts with met-enkephalin.
- 4 This antiserum is directed to the C-terminal tetrapeptide common to gastrin and cross reacts with CKK.
- 5 This antiserum is an antiserum probably containing several antibodies to GIP.
- 13 All SP-antisera cross react with tachykinins such as physalaemin and eledoisin.
SP 8 does not cross react with bombesin or GRP.
K 16 cross reacts with bombesin.

Table II. Clinical and biochemical data on 16 patients with ileal carcinoids and liver metastases.

Patient	Sex	Primary tumor no size	Carcinoid syndrome	5-HIAA/u $\mu\text{mol}/12$	5-HT/ppp ng/ml ³	5-HT/whole blood ng/ml ⁴	Substance P pmol/ ¹⁵	Follow-up
1	M	mult	?	151	17	-	-	Alive after 4 years
2	M	solit	?	44	15	-	19	"
3	F	mult	1-2 cm	113	73	814	-	Dead after 1 1/2 years
4	F	mult	>2 cm	120	31	813	7	Alive after 2 years
5	F	mult	>2 cm	2 149	1 134	975	427*1)	Alive after 2 1/2 years
6	M	solit	?	41	12	246	0	"
7	M	mult	1-2 cm	128	184	486	35*	Dead after 2 years
8	F	solit	>2 cm	330	107	1 116	13*1)	"
9	F	solit	1-2 cm	1 210	163	-	-	Dead after 1 year
10	M	solit	1-2 cm	44	56	1 977	210	Alive after 7 years
11	M	solit	<1 cm	490	-	869	81	Alive after 2 years
12	F	solit	>2 cm	870	116	1 058	50	"
13	F	solit	1-2 cm	1 760	-	1 022	65	Alive after 1 year
14	M	mult	>2 cm	2 700	89	-	-	Dead after 1 year
15	M	mult	1-2 cm	112	-	-	-	Dead after 1 month
16	M	solit	<1 cm	1 120	68	1 047	152	Dead after 2 years

* Data from (23).

Normal range 1) Hepatic venous blood. 2) < 80. 3) Male 2 ± 1 , female 2 ± 1 . 4) Male 124 ± 13 , female 103 ± 15 . 5) 9 ± 3 .

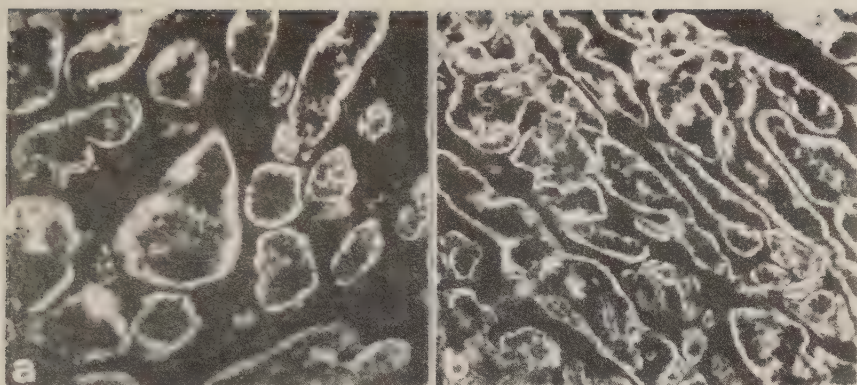


Fig 1. Sections from a primary tumor. The tumor tissue was processed for the fluorescence histochemical demonstration of serotonin. The two sections cut from different portions of the tumor illustrates variability in growth pattern being mostly insular in a) and trabecular in b). (x 150)

In 2 patients specimens from both the primary tumor, the lymph node metastases and the liver metastases were examined. In 3 patients we examined both a primary tumor and liver metastases, and in 1 patient lymph node and liver metastases were analyzed. From 8 patients only liver metastases were examined and from 2 patients we only received lymph node metastases (Table III).

The growth pattern of the primary tumors was insular, trabecular or a mixture of both (Table III, Fig 1). The lymph node metastases had essentially the same pattern while some liver metastases also had acinar or undifferentiated growth. The growth pattern in the primary tumor and in secondaries in lymph nodes or in the liver was generally very similar. However, in one primary tumor with insular growth pattern the liver metastasis displayed undifferentiated growth.

The histofluorescence investigation revealed dense accumulation of serotonin containing cells in all tumors regardless of whether they were primary tumor, lymph node or liver metastases. The intensity of the serotonin fluorescence was generally similar in the primary tumor and in corresponding secondaries, except in 1 case where the metastasis from the liver displayed a distinctly weaker fluorescence than the corresponding primary tumor.

Table III. Growth pattern, amine and peptide content in ileal carcinoid tumors.

Patient	Primary tumor Growth pattern	5-HT ¹⁾	Substance pI)	Other peptides ¹⁾	Lymph node metastasis Growth pattern	5-HT ¹⁾	Substance pI)	Other peptides ¹⁾	Liver metastasis Growth pattern	5-HT ¹⁾	Substance pI)	Other peptides ¹⁾
1	-	-	-	-	insular	+++	+	0	insular	+++	+	0
2	-	-	-	-	-	-	-	-	insular	+++	+	0
3	-	-	-	-	-	-	-	-	insular/ trabecular	+++	0	0
4	insular/ trabecular	+++	++	0	-	-	-	-	trabecular/ insular	+++	+	0
5	insular/ trabecular	+++	++	enkephalin +	-	-	-	-	trabecular	++	+	0
6	-	-	-	-	-	-	-	-	insular	+++	+	0
7	-	-	-	-	insular/ acinar	+++	++	0	-	-	-	-
8	-	-	-	-	-	-	-	-	mixed	+++	+	0
9	-	-	-	-	0	+++	+	0	-	-	-	-
10	-	-	-	-	-	-	-	-	insular/ acinar	+++	+	0
11	-	-	-	-	-	-	-	-	insular	+++	+	0
12	-	-	-	-	-	-	-	-	undiff	+++	++	0
13	insular/ trabecular	+++	+	0	-	-	-	-	trabecular	+++	+	0
14	trabecular	+++	+	0	insular	+++	+	0	insular	+++	+	0
15	-	-	-	-	-	-	-	-	insular/ anapl	+++	+	0
16	insular	+++	++	0	insular/ trabecular	+++	+	0	undiff	+++	+	0

1) Intensity of fluorescence or immunoreaction: +++ = intense; ++ = moderate; + = weak; 0 = no.

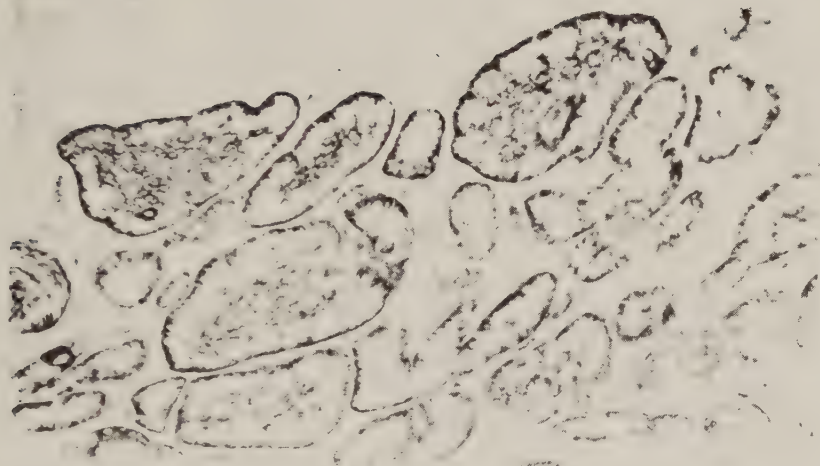


Fig 2. Immunocytochemical demonstration of substance P (PAP technique) in section from the same tumor as in Fig 1. Most tumor cells display substance P immunoreactivity of varying intensity. Normal mucosal epithelium at the top of the figure. (x 150)

In all tumor examined except for one liver metastasis we found numerous substance P immunoreactive tumor cells (Table III, Fig 2). These cells invariably constituted the majority population of the tumor cells. However, there was a difference between the primary tumors and the metastases. The majority of the primary tumors examined displayed moderate substance P immunoreactivity while only very few lymph node and liver metastases showed a comparable intensity of substance P immunostaining. The majority instead showed a weak immunoreactivity (Table III).

Of the other 14 peptide antisera tested (Table I) only the enkephalin antiserum gave positive results in 1 primary tumor. Here only few scattered tumor cells were immunoreactive. In the liver metastases of this patient no enkephalin immunoreactive cells could be detected.

DISCUSSION

The malignant potency of the carcinoid tumor has been debated for many years. So far, the size of the primary tumor has been shown to be correlated with the extent of metastatic growth and, in addition, with survival (24, 25, 26, 27, 28). The localization of the primary tumor is also important with respect to the prognosis (25, 27). Recently the histological growth pattern has also been claimed to be of prognostic value (29). It is a common experience among surgeons that patients with widespread tumor growth may survive for 10-20 years. This might indicate that the biological tumor activity has dimensions other than size, site and structure. The content of peptides could be one of them. Several studies, including the present indicates that one major peptide in midgut endocrine tumor is substance P (4, 7, 8, 9, 12).

In the present study, in which the tissues were treated under optimal conditions for immunocytochemistry and histofluorescence, we found serotonin-containing cells in all tumors, substance P immunoreactivity in 15 of 16 tumors and enkephalin immunoreactivity in one tumor that also stored substance P. The difference in results compared to other studies claiming the existence also of other neurohormonal peptides (10, 11, 13) may be explained by different composition of the tumor material, different types of tissue fixation and/or different specificity of the antisera. The lack of multiple neurohormonal peptides differs strikingly from the results obtained on foregut and hindgut tumors by several authors (1, 3, 30, 31, 32, 33, 34). As there seems to be very little variation in peptide content of the midgut tumors, the peptides can probably not serve as markers for biological activity. The density of serotonin fluorescent cells was similar in all tumors regardless of whether they were primaries or secondaries while the density of substance P immunoreactive cells and the intensity of their immunostaining were less in the secondaries. This discrepancy may be due to a difference in growth rate between primary tumor and metastases.

The histological growth pattern has been claimed to be related to survival in that undifferentiated and glandular growth patterns are associated with poor prognosis whereas insular, trabecular or a mixed growth pattern are connected with better survival rate (29). Even if the tissue material analyzed in that study was homogeneous in the sense that all specimens were from patients with metastatic disease no subdivision of the tumors in foregut, midgut or hindgut tumors was done. Furthermore, the primary tumor site was unknown in 1/3 of the cases. In the present study on 16 metastatic midgut tumors, the growth pattern does not seem to relate to survival rate. In the 5 patients where we were able to analyze both primary and metastatic tumors some differences in growth pattern were noticed. It may therefore be important to know from where the specimens for analysis are taken.

The tendency of the primary carcinoid tumors in the ileum to be

multiple has been shown in several studies (25, 26, 35). In general one third of the patients have multiple primary tumors, and in the present series we can confirm this tendency as 7 of 16 cases (44 %) were multiple.

In the detection and follow-up of carcinoid tumors measurement of 5-HIAA in urine has been claimed to be a good marker (36, 37). In previous studies we also found that serotonin in platelet-poor plasma was a reliable tumor marker and a good criterion of tumor size and activity (37, 38). The present study supports these findings (Table III) and in addition we found high levels of serotonin and substance P in whole blood and plasma, respectively.

To conclude, we have shown that the midgut carcinoid tumors, when compared with carcinoids arising in foregut and hindgut, are strikingly homogeneous. They invariably store serotonin, almost invariably substance P and only occasionally an additional peptide (enkephalin). The histological growth pattern, on the other hand, was found to vary widely. We have in the present study not been able to distinguish any single factor of importance to determine the biological activity of the carcinoid tumor. However, a closer analysis of growth patterns in primary and metastatic tumors may be a better tool. The ultrastructural features of the tumor cells, notably the size and morphology of the secretory granules, may be an additional criterion allowing subclassification of midgut tumors.

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ELEVATED CONCENTRATIONS OF SUBSTANCE P AND 5-HT IN PLASMA IN PATIENTS
WITH CARCINOID TUMOURS

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SUMMARY

Ten patients with metastatic carcinoid tumours in the liver showed elevated 5-hydroxytryptamine and substance P levels in plasma samples taken from hepatic or peripheral veins. Chromatographic characterization of the substance P-immunoreactivity showed that by gel permeation and high pressure liquid chromatography the substance P-immunoreactivity was indistinguishable from synthetic undecapeptide substance P. The results suggest that substance P, in addition to the 5-hydroxyindoles, may serve as a circulatory marker for some forms of carcinoid tumours.

INTRODUCTION

Carcinoid tumors arise from enterochromaffin cells and some are known to contain both 5-hydroxytryptamine (5-HT) and substance P-like immunoreactivity (SPLI) (1, 2). It is well established that 5-HT is secreted from carcinoid tumours and that elevated blood levels of 5-HT are often found in carcinoid patients (2, 3, 4, 5). It thus seemed likely that at least some tumours would also secrete SPLI. A preliminary report has indeed indicated the existence of elevated levels of SPLI in plasma from carcinoid patients (6). The present study involved measurements of the blood and plasma levels of 5-HT and SPLI in 10 carcinoid patients, and characterization of circulating SPLI as the undecapeptide substance P in plasma samples from carcinoid patients.

MATERIALS AND METHODS

Patients

Ten patients with metastatic carcinoid tumours of midgut origin were investigated (Tables 1 and 2).

Sample collection

Blood was collected from peripheral and hepatic veins. Hepatic venous blood was obtained from a caval catheter placed in the right hepatic vein. For the determination of 5-HT in whole blood and platelet-poor plasma (PPP), 4 ml and 8 ml blood, respectively, were collected in ice-chilled tubes containing EDTA and ascorbic acid as protective agents. The PPP was produced by a two-step centrifugation procedure and the number of platelets in our PPP preparations averaged 10×10^9 /litre plasma (normal platelet count $179-300 \times 10^9$ /litre plasma) (for details of methodology see Nobin et al (5)).

For the measurement of SPLI 7 ml of blood was withdrawn into glass tubes containing 1 ml saline with 2 mM parachloromercuribenzoic acid (to inhibit peptidase activity), EDTA and ascorbic acid. After centrifugation (400 g, 10 min, 7°C) 2 ml of the supernatant was added to an equal volume of boiling 2 M acetic acid. After boiling for 10 min the samples were again centrifuged (10 000 g, 20 min, 4°C) and the supernatants freeze-dried.

Analytical methods

5-HT determinations were performed with high pressure liquid chromatography and electrochemical detection as described by Nobin et al 1982 (5). For analysis of substance P the freeze-dried samples were reconstituted in water and applied to small Amberlite XAD-2 columns (5 ml) (7). After extensive washing (40 ml water) to remove salts and non-adsorbed material the adsorbed substance P was eluted (70-90 % recovery of substance P standards) with 6 ml of an acetone/0.01 N HCl

Table I. Data on five carcinoma patients with liver metastasis and concentrations of substance P and 5-HT in peripheral venous blood.

Pat No	Age	Sex	Symptoms at time of biochemical analysis	Substance P pmol/l plasma	5-HT µg/l PPP	5-HT µg/l blood	5-HIAA µmol/24 h in urine
1	72	M	Abdominal pain/diarrhoea	35	49	572	120
2	52	M	Carcinoid syndrome	52	59	949	173
3	63	M	None reported (although liver metastasis found)	25	11	262	128
4	76	M	Carcinoid syndrome	137	274	1 039	257
5	58	M	Carcinoid syndrome	200	190	918	360
Carcinoid patients mean and range							
				90 (25-200)	117 (11-274)	748 (262-1 039)	208 (120-360)
Normal controls mean $\pm$ SEM							
				9 $\pm$ 3 (n=10)	3 $\pm$ 2 (n=16)	113 $\pm$ 32 (n=22)	<80 (n=22)

Table II. Data on five carcinoid patients with liver metastasis and concentrations of substance P and 5-HT in hepatic venous blood.

Pat No	Age	Sex	Symptoms at time of biochemical analysis	Substance P pmol/l plasma	5-HT $\mu\text{g/l}$ PPP	5-HT $\mu\text{g/l}$ blood	5-HIAA $\mu\text{mol/24 h}$ in urine
6	60	F	Carcinoid syndrome	161.4	17	587	47
7	58	M	Carcinoid syndrome	175.8	257	1 005	360
8	62	M	Carcinoid syndrome	177.3	139	395	141
9	68	F	Carcinoid syndrome	426.8	1 333	975	2 149
10	64	F	Carcinoid syndrome	12.8	73	927	330
Carcinoid patients mean and range							
				234 (13-427)	324 (73-1 133)	778 (395-1 005)	604 (47-2 140)
Normal controls mean $\pm$ SEM							
				-	2+3 (n=8)	117+21 (n=8)	<80 (n=22)

(80/20 v/v) solution. The acid acetone was evaporated and the samples reconstituted in barbitural buffer for substance P radioimmunoassay, using either N- or C-terminal directed antibodies (8). The specificity of the substance P diverted antisera used has been described in detail, however, in brief the amino-terminal directed antisera (N-terminal) recognizes only substance P and its free acid; removal of any of the amino-terminal aminoacids results in loss of cross-reactivity (8). Similarly the carboxy-terminal directed antisera (C-terminal) recognizes the presence of the methionine amide and at least five of the carboxy-terminal aminoacids of substance P. The presence of equivalent amounts of N- and C-terminal immunoreactivity taken together with chromatographic evidences (see later) is likely to indicate the presence of the intact substance P undecapeptide. The material remaining after initial substance P radioimmunoassay was pooled and chromatographed on a Bio-Gel P-2 column (1 cm diameter x 25 cm). The substance P immunoreactivity recovered from the Bio-Gel P-2 column was separated further on a Waters series 600 chromatograph using a C₁₈ μ -Bondapal analytical column and a 5 % to 65 % gradient of acetonitrile in 10 mM ammonium acetate (pH 4.0) (9). Urine was collected for 24 h and the excretion of 5-hydroxyindoleacetic acid (5-HIAA) was measured by a spectrophotometric method (10).

RESULTS

The mean content of substance P in the peripheral venous plasma samples from five carcinoid patients was 89.9 pmol/l (range 25-200 pmol/l) and the 5-HT content of whole blood and PPP was 748 μ g/l (range 262-19 μ g/l) and 117 μ g/l (range 11-274 μ g/l) (Table I). The urinary excretion of 5-HIAA of these patients were above the upper limit of normal. Determinations carried out on peripheral plasma samples from normal volunteers indicated that the normal content of SPLI was less than 10 pmol/l (9 ± 3 pmol/l $n = 10$) and that of 5-HT in whole blood and PPP was 113 ± 32 μ g/l ($n = 22$) and 3 ± 2 μ g/l ($n = 16$), respectively.

The analysis of the substance P content in the hepatic venous plasma samples from carcinoid patients (patient Nos 6-10, Table II) showed a mean concentration of 234 pmol/l (range 13-427 pmol/l). One of these patients (no 10), however, had a substance P concentration that was clearly below the others, and this value was in the normal range (Table I). In the five carcinoid patients the values for 5-HT in whole blood (mean = 778 μ g/l, range 395-1 005 μ g/l) and in PPP (mean = 324 μ g/l, range 73-1 133) from hepatic venous samples were above the normal limits. The normal values for 5-HT were not significantly different in peripheral and hepatic venous blood or plasma. The 5-HIAA excretion was increased in four of these carcinoid patients.

Characterization of the substance P immunoreactivity from the hepatic venous plasma of patients no 6-10 by serial dilution indicated that in both the C-terminal assay (Fig 1 A) and N-terminal assay (Fig 1 B) the

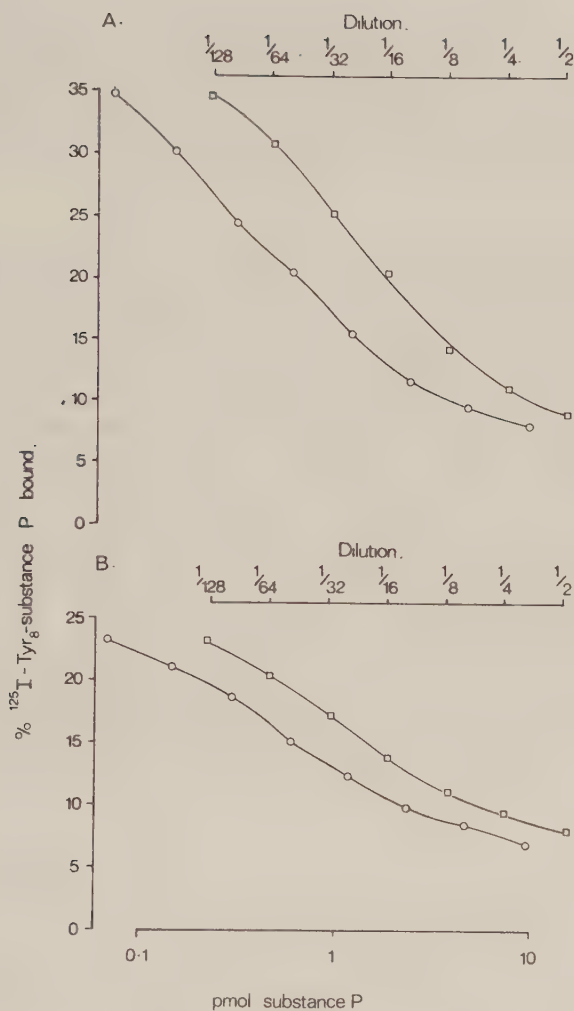


Fig 1. Serial dilution in the substance P radioimmunoassay of substance P like material from the plasma of carcinoid patients (nos. 6-10) using A an antiserum recognizing the carboxy-terminal region of substance P and B an antiserum recognizing the amino-terminal regional of substance P. Note the correspondence of the quantities of substance P detected in both radioimmunoassays and the parallel dilution with standard synthetic substance P. O = synthetic substance P, □ = carcinoid plasma.

SPLI behaved like synthetic substance P. Further chromatography on Bio-Gel P-2 yielded one peak of SPLI eluting from the column at the position of the undeca-peptide substance P (data not shown). Application of this peak of SPLI to the HPLC column showed that the SPLI material present separated in the position expected for the undeca-peptide substance P and that equal amounts of immunoreactivity were detected by both N-and C-terminal directed assays (Figs 2 A and B).

DISCUSSION

This study demonstrates the presence of relatively high concentrations of the undeca-peptide substance P in hepatic and peripheral venous plasma of patients with carcinoid tumours of midgut origin. Nine out of ten carcinoid patients studied had substantially elevated circulating substance P levels, which is in line with our immunohistochemical observations that most midgut carcinoid tumours contain substance P (unpublished observations). All patients studied also had significantly increased 5-HT levels in blood and plasma and nine patients showed increased urinary excretion of 5-HIAA. The presence of only very low or undetectable amounts of SPLI in the peripheral venous plasma of normal volunteers suggests that the presence of SPLI in plasma at concentrations well in excess of 10 pmol/l may indicate the presence of a carcinoid tumour (although the possibility of other tumour cell lines secreting SP cannot be discounted). If so, plasma SP measurements may prove to be a useful complement to measurements of 5-HT as a diagnostic tool for detecting carcinoid tumours. Recent results have shown that circulating hormone levels may be used to evaluate the effectiveness of therapy in the treatment of endocrine pancreatic tumors (12). Similarly the extent and activity of carcinoid tumors has been correlated with circulating amine levels (2). However, it remains to be established whether plasma substance P levels can also be used to monitor the development or regression of ileal carcinoids.

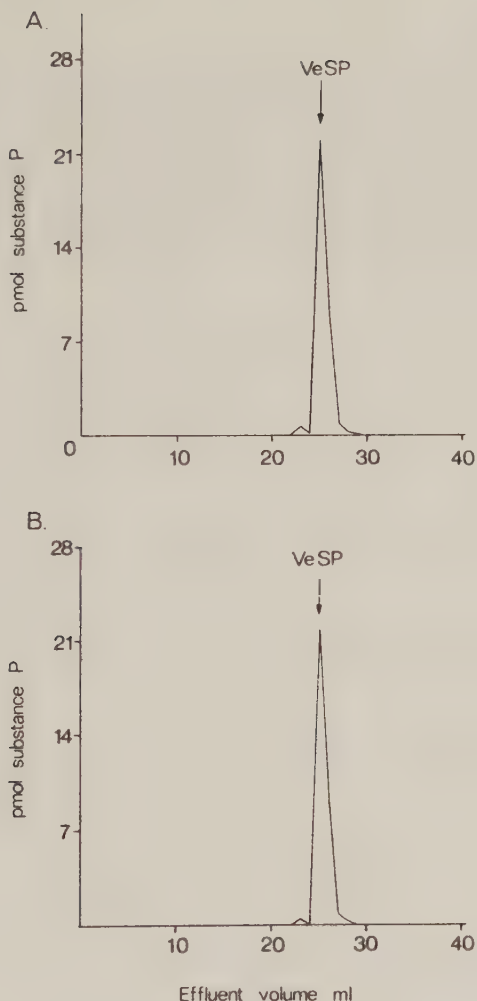


Fig 2. High pressure liquid chromatography (HPLC) of SP-like material obtained from gel filtration of plasma extracts from carcinoid patients (nos. 6-10). The HPLC was performed as described in the methods and the substance P content determined using antisera recognizing the carboxy terminal sequence (A) or the amino terminal sequence (B) of substance P. The elution position of synthetic undecapeptide substance P is denoted by the arrows (VeSP).

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Angiographic and Computed Tomographic Appearance of Secondary Carcinoid of the Liver

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Abstract. Liver angiograms of 27 patients with hepatic carcinoid metastases were analyzed for distribution, size, degree of vascularity, and patterns of tumor staining. Computed tomography (CT) scans were evaluated before and after bolus contrast administration in 13 of the cases. The diagnostic capability of the two procedures was compared. Angiography detected metastases, some less than 1 cm in size in all 13 patients; in 5 of 13 cases (38.5%) CT did not detect any hepatic metastases. In the eight patients in whom CT demonstrated metastases, the patterns of lesions and usefulness of contrast varied. Angiography is essential for evaluation of patients with suspected carcinoid metastases to the liver.

Key words: Carcinoid tumor – Liver metastases – Angiography – Computed tomography

Patients with the carcinoid syndrome usually have hepatic metastases from a carcinoid tumor [1]. Remission of symptoms has been achieved by various treatment regimes including liver resection, hepatic dearterialization, embolization and ⁶⁰Co radiation therapy [2-5]. Prior to treatment it is of great importance not only to establish the presence of metastases but also their distribution and extent. These data are valuable in determination of the method of treatment as well as for follow-up of tumor regression after treatment.

There have been only a few reports, however, on the diagnosis of metastatic carcinoid [6]. The com-

puted tomographic (CT) appearance of hepatic carcinoid metastases has been reported in only one case as far as we know [7]. Twenty-seven patients with hepatic carcinoid metastases have been examined at the Department of Diagnostic Radiology, University Hospital, Lund, Sweden, with angiography in all cases, and in 13 cases also with CT.

In this paper we review and analyze the angiographic and computed tomographic appearance of secondary carcinoid of the liver. In addition, the diagnostic ability of these procedures for detecting metastatic carcinoid is compared.

Material and Methods

Twenty-seven cases with hepatic metastases from carcinoid tumors were studied. The diagnosis was proven at surgery or biopsy in all instances. The location of the primary carcinoid was distal ileum in 25 cases, jejunum and rectum in one case each. Angiography was performed in all patients and CT scans in 13.

Angiography of the liver was usually performed as follows (1) *Celiac arteriography*: frontal and right posterior oblique position with injection of 40 ml of Isopaque Coronar (350 mg I/ml 6-10 ml per second, and exposures one per second for two seconds, two per second for five seconds, and one exposure every other second for eight seconds; and (2) *Common hepatic arteriography*: 50 ml of Isopaque Coronar 3-5 ml per second, 16 films over 32 seconds. In addition, when there was an accessory hepatic artery, superior mesenteric arteriography was also performed with an injection of 40 ml of Isopaque Coronar, 10 ml per second, 16 films over 15 seconds with exposures as mentioned under (1).

The angiographic features were analyzed with regard to distribution, size, degree of vascularity, and patterns of hepatic tumor staining. In addition, occlusion or narrowing of the portal vein was noted.

Hepatic CT scans were performed with a Philips Tomoscan 300 (slice thickness 12 mm, scan time 4.2 sec) before and after intravenous bolus injection of contrast medium. Plain CT scans were performed with 8 to 10 slices at 18-mm intervals through the entire liver. Repeat CT scans were then performed at selected levels after bolus injections of 30-50 ml of Isopaque Cerebral (280 mg Iodine), injected over a period of 5-10 sec into the femoral vein. Scanning was started approximately 15 sec after completion of the injection.

The distribution and size of hepatic metastases were evaluated

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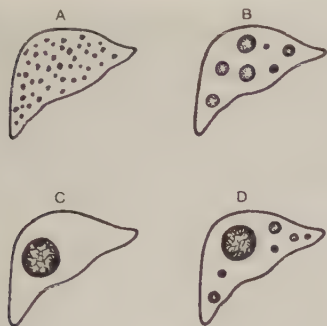


Fig. 1A-D. Distribution of hepatic carcinoid metastases. **A** Fine nodular (four cases). **B** Coarse nodular (14 cases). **C** Single large mass (four cases). **D** Single large mass and coarse nodular (five cases).

on CT scans. The attenuation of the lesion and normal liver, respectively, were measured using a region of interest (ROI) cursor. Measurements were performed before and after contrast in three or more areas which were free of artifact. The mean values were reported.

Distribution and size of hepatic metastases were quite variable at angiography. The lesions, however, were classifiable into four basic types: fine nodular dissemination, coarse nodular, single mass, and a combined single mass and coarse nodular type (Fig. 1).

The vascularity of hepatic carcinoids was categorized as four types in accordance with degree of neovascularization. Lesions with no visualized neovasculature were considered hypovascular (-). When neovascularity was present, it was divided into three

categories: slight (+), moderate (++) , and marked hypervascularity (+++).

The hepatic metastases showed different angiographic appearances of staining which were divided into four patterns: homogeneous, ring-like, mottled, and lucent. The lucent pattern was characterized by areas of lucency against the background of the hepatogram, while the remaining three patterns demonstrated areas of increased density when compared with the surrounding hepatic parenchyma. The findings at angiography and at CT examination were compared.

Results

Angiographic Appearance

Angiography detected hepatic metastases of carcinoid tumors in all cases. Fine nodular dissemination was present in four cases, with multiple small nodules less than 1 cm in diameter disseminated throughout the entire liver (Figs. 1 and 2). The multinodular type was most frequent in this series (14 cases). Round nodules ranging in size from less than 1 cm to 5 cm in diameter were distributed throughout both lobes of the liver. Of these 14 cases, the nodules were very numerous in nine cases and considerably less numerous in five cases (Fig. 3).

A single metastasis was seen in four cases. All four were located in the right hepatic lobe. In two of these cases, although the lesions represented the confluence of several nodules, they were localized as a solitary mass with no other separate metastases. Therefore, they were classified into the single nodule category. The size of the masses ranged from 7.5

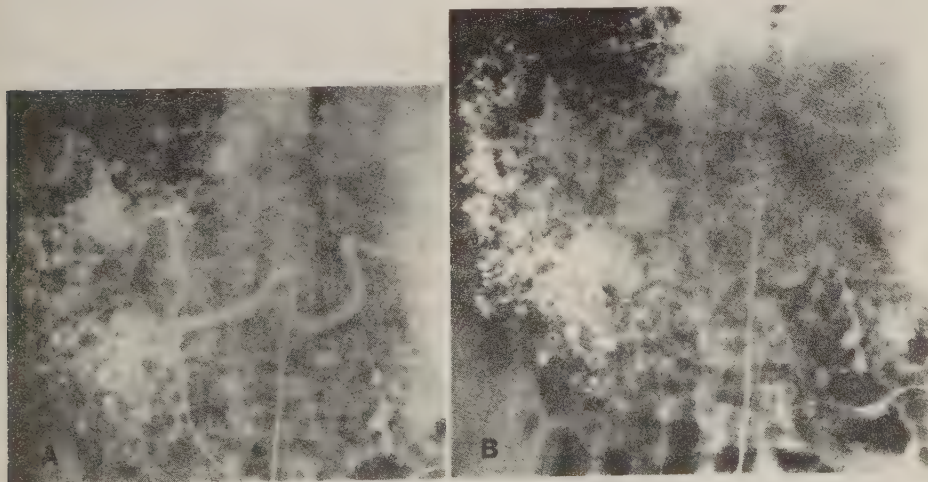


Abb. 2A, B. Fine nodular carcinoid metastasis. **A** Arterial phase; and **B** parenchymal phase

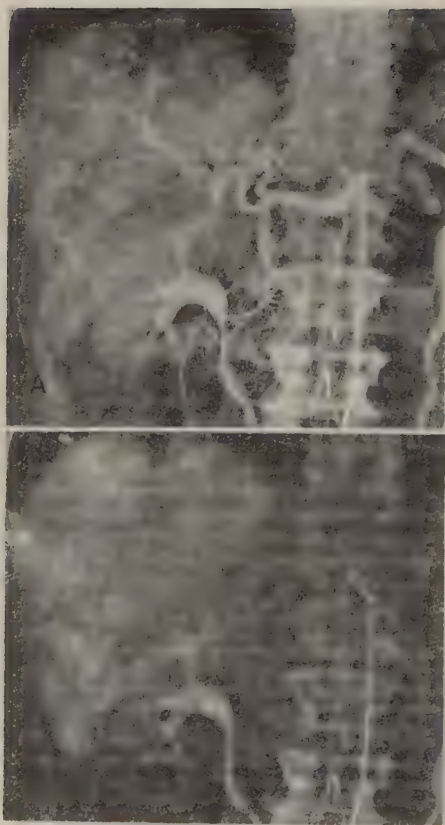


Fig. 3 A, B. Coarse nodular carcinoid metastasis. A Arterial phase; and B parenchymal phase.

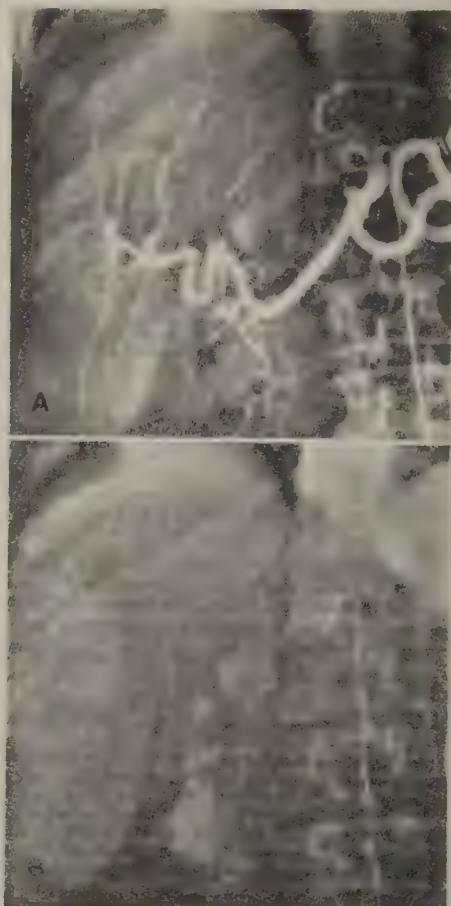


Fig. 4 A, B. Large single carcinoid metastasis. A Arterial phase; and B parenchymal phase.

to 18 cm in diameter (Fig. 4). The combined single mass and multinodular type was observed in five cases in which a large mass over 8 cm in diameter was present with other multiple small nodules. In two of these combined cases, the large masses were more than 15 cm in diameter (Fig. 5).

As shown in Table 1, four cases were markedly hypovascular. Vascularity was slight in 11, moderate in 10, and hypervascular in two cases. Two hypervascular tumors were of the combined single and multinodular type with a large mass more than 15 cm in

diameter. The angiographic appearance of these tumors was quite similar to that seen in hepatoma. In fact, one of these hypervascular tumors demonstrated arteriovenous shunting and pooling and was impossible to differentiate from hepatoma (Fig. 5). The four hypovascular tumors were multinodular and fine nodular dissemination was present in two cases each.

The metastases were best demonstrated during the capillary rather than the venous phase. The pattern was homogeneous in 17 cases, ring-like in 11, mottled

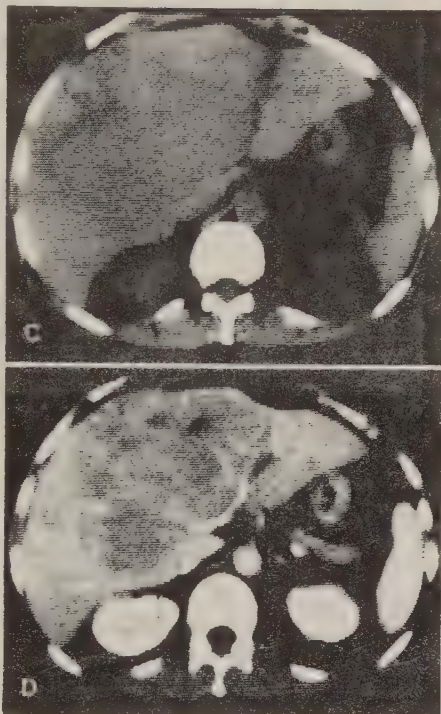
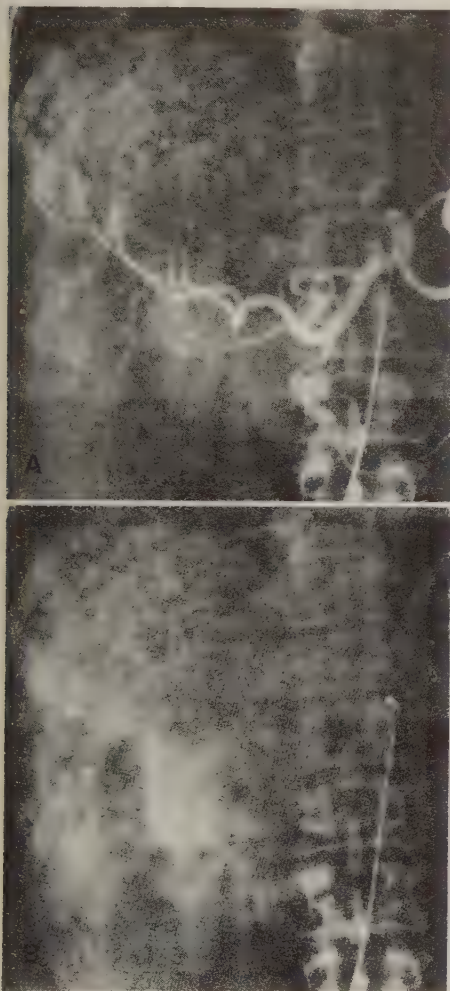


Fig. 5A-D. Combined single mass and multi-nodular metastasis of carcinoid tumor. Angiographic findings in the large mass mimic hepatoma. **A** Arterial phase; **B** parenchymal phase; **C** non-enhanced CT examination shows slightly reduced density in large tumor; **D** contrast-enhanced CT examinations gives improved outlining of tumor with increased density in periphery of tumor.

in 13, and lucent in two cases (Table 1). In 48% of the cases, two or three patterns of staining were present at the same time. However, the homogeneous pattern was most frequent in this series and 10 cases showed only the homogeneous pattern of staining. In addition, most lesions under 2 cm in diameter were of the homogeneous pattern, and when the size was 3-5 cm there was a tendency toward a mottled or ring-like appearance.

Computed Tomographic Appearance

Diagnostic Ability. CT scans were performed in 13 of 27 cases in this series. Hepatic metastases were not detected at CT in five cases (38.5%), neither before nor after the bolus injection of contrast medium, despite evidence of metastases on the angiograms. Three of these cases were of the multinodular type with metastases ranging in size from 1 to 5 cm in

Table 1. Angiographic appearance of hepatic carcinoid metastases in 27 cases

Angiographic findings	No. of cases
Degree of vascularity	
Hypovascular (-)	4
Slight (+)	11
Moderate (++)	10
Hypervascular (+++)	2
Patterns of staining ^a	
Homogeneous	17
Mottled	13
Ring-like	11
"Lucent"	2
Patency of portal vein	
Patent	21
Compressed { main stem	3
{ only intrahepatic branch	3
Occluded	0

^a In 48% of cases, two or three patterns of staining were present at the same time

diameter. The vascularity was slight in two cases and moderate in one. The remaining two cases were of the fine nodular dissemination type (Fig. 6). The staining pattern in all of the five cases missed by CT was homogeneous, except for one 5-cm lesion which showed the mottled pattern.

The CT scans detected hepatic metastases in 8 of 13 cases (61.5%). When compared with the angiographic appearance, four of these cases were of the combined single and multinodular type with a large mass ranging 7 to 20 cm in diameter; three of these cases were demonstrated by CT as areas of low density both before and after contrast administration and in the fourth case there was diffuse contrast enhancement around the periphery of the low-density lesions (Fig. 5). The angiographic pattern of staining of these four masses was ring-like in the former three cases and mottled in the fourth case. The multiple nodules associated with the large masses, however, were not as distinct as they appeared on the angiograms. In the remaining four cases detected by CT, one had a single mass with a mottled pattern of staining and three cases were of the multinodular type, including the one case which was ultimately detected as areas of low density only after contrast injection (Fig. 7).

The CT-Attenuation Value of Hepatic Metastases. In seven cases, the hepatic metastases were detected by both pre- and postcontrast CT scans. The precontrast CT number of these lesions ranged from 13 to 43 Hounsfield Unit (HU), with an average of 34. The difference between the CT number of the liver and the lesions was 10–34 HU. After the bolus injection

of contrast medium, the CT number of the lesion increased from 19 to 42 HU, except in one case which increased only 5 HU. This last CT scan demonstrated a large mass with an avascular (ring-like) center on angiograms.

The attenuation difference between the liver and the lesions after contrast also increased, ranging from 26 to 45 HU in five of seven cases. In the remaining two cases, however, the attenuation difference decreased from 31 HU to 20 HU, and from 15 HU to 7 HU, respectively. One case which was isodense on precontrast scans was ultimately demonstrated as an area of low density after contrast administration; the difference between the CT number of the normal liver and this lesion after contrast was 7 HU. At angiography this case was of the multinodular type in distribution with the tumor size ranging from 1 to 2 cm. The degree of vascularity was slight (+), and there was a homogeneous pattern of staining.

Discussion

Primary carcinoid tumors of the ileum may produce markedly different distribution patterns of liver metastasis; varying from a single large mass to fine nodular dissemination. Three types of hepatic metastases of ileal carcinoid tumor have been reported; solitary large metastasis, multiple nodules of varying size, and minute metastases distributed throughout the liver [6]. In our series in addition to these three types, a combined single mass and multinodular type was noted in 6 of 27 cases (22.2%).

The occurrence of this additional tumor type is of diagnostic significance because differentiating it from a single mass is important in determining resectability of the lesion. Before one diagnoses a single, and hence potentially resectable carcinoid metastasis, careful evaluation should be made to rule out the presence of other smaller nodules. Notably this combined single and multinodular type of carcinoid metastasis is quite similar to the tumor distribution seen in solitary hepatoma with intrahepatic metastases.

It is generally thought that the hepatic carcinoid metastases possess a rich vascular supply with a higher degree of vascularity than the original tumor in the bowel [6]. The majority of our cases (78%) revealed slight (+) to moderate (++) neovascularity. The degree of vascularity is likely related to tumor size, increasing as the tumor enlarges, unless there is extensive necrosis within the lesion. In fact, one large 20 × 22 cm hypervascular metastasis in this series, simulated a hepatoma with pooling and arteriovenous shunting (Fig. 5). In contrast to this, however, there was one exceptional multinodular type of tumor

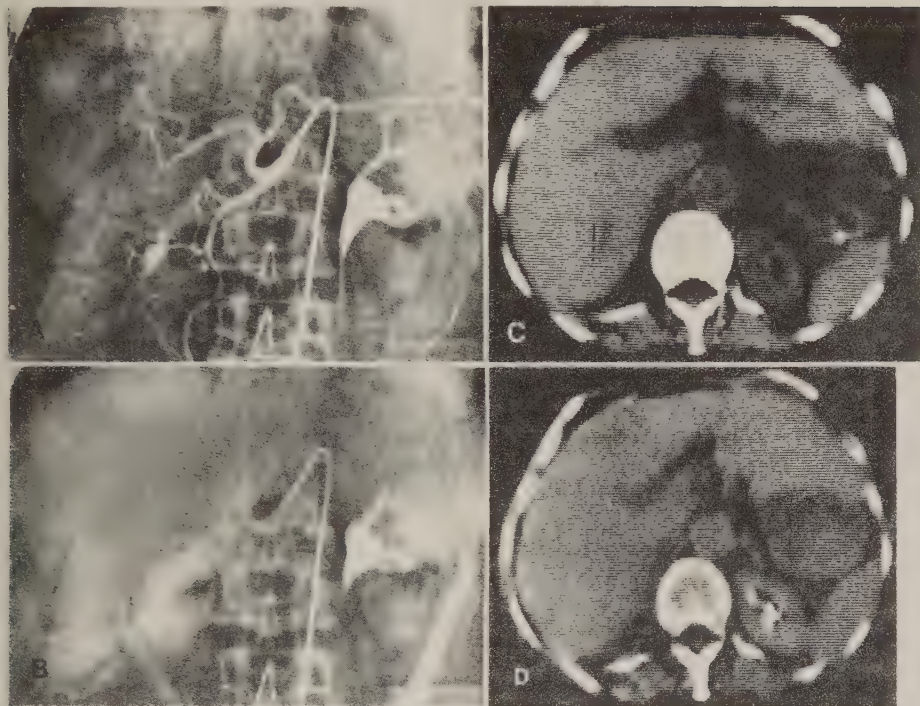


Fig. 6A–D. Fine nodular carcinoid metastasis. **A** Arterial; **B** parenchymal phase; **C** non-enhanced CT examination; and **D** contrast-enhanced CT examination. The area of slightly decreased attenuation seen anteriorly in the right lobe in **C** and **D** has too low a difference in attenuation (6 Hounsfield Unit) to be diagnostic for metastasis and in this case has been judged to be an artifact caused by rib-shadowing.

which was hypovascular; showing areas of lucency against the hepatogram.

Hypovascular carcinoid metastases have been reported and can be very difficult to differentiate from cholangiocarcinoma [8]. Hence, hypovascular hepatic carcinoid metastases offer an additional diagnostic consideration in the angiographic evaluation of hepatic metastases.

Hepatic metastases of carcinoid show dense tumor staining at angiography [6, 8, 9]. Tumor staining was observed in all of our cases except the one hypovascular tumor described above. Tumor staining is probably caused by contrast medium that is both in numerous fine vessels, and within the tumor parenchyma detectable due to "leaky" capillaries with extravasation of contrast. Hence, the various angiographic patterns of tumor staining to some degree, reflect histologic changes within the tumor itself.

Four different staining patterns were observed:

homogeneous, mottled, ring-like, and "lucent." The homogeneous pattern was most frequent (40%). Mottled or ring-like staining was more often observed with increasing tumor size. These two patterns are probably related to tumor necrosis. This would also explain the low CT attenuation values measured within mottled and ring-like lesions. It hence can be postulated that the observation of angiographic tumor staining patterns may offer a means of evaluating tumor growth, or regression after treatment.

The maintenance of portal vein patency depends mostly upon the location and size of the tumor (Table 1). It is necessary to know whether the portal vein is occluded prior to treatment, especially before dearterialization or embolization of the hepatic artery, since the normal liver parenchyma survives the ischemic period only by portal blood supply [5, 10].

Computed tomography failed to detect hepatic metastases in 5 of 13 cases even after bolus injection

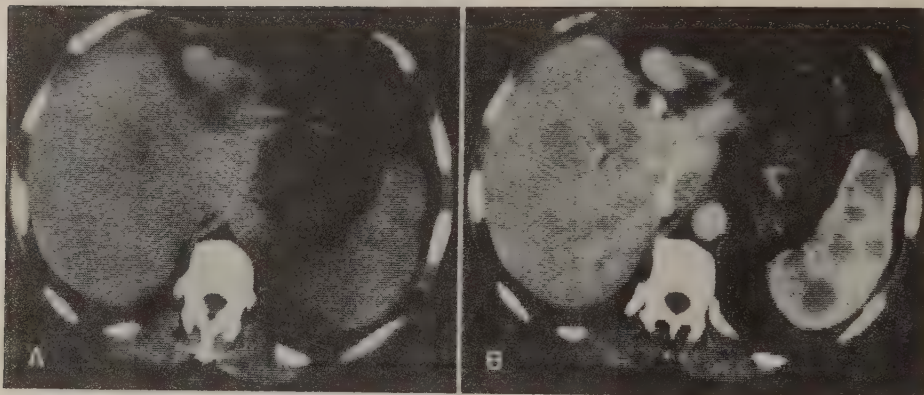


Abb. 7A, B. CT examination of patient with multiple carcinoid metastases in liver and spleen. A Nonenhanced examination does not demonstrate metastasis. B Contrast-enhanced examination show metastasis in liver and spleen.

of contrast medium. In two of these, the metastases were of the fine nodular dissemination type with tumor size less than 1 cm in diameter; hence the inability of CT to detect these metastases may be due to their very small size. However, in the three remaining patients in whom CT failed to detect metastases, the lesions were 1–5 cm in diameter. This may be caused by faulty timing of intravenous injection of contrast (15–20 sec). It is possible that the metastases could have been detected by another time interval bolus scan and most probably they could have been detected by using sequential scanning after bolus injection. At the present time we have had no opportunity to perform sequential scanning.

Of the eight cases detected by CT, the results were quite variable. Contrast administration was not always effective for detection of metastases. Most of the CT detectable cases were of the ring-like or mottled appearance at angiography, indicating the presence of some necrotic areas within the lesion, while the tumors missed by CT were mostly of the homogeneous staining pattern. This indicates that the detectability of hepatic carcinoid by CT is greatly dependent upon the presence and size of tumor necrosis area.

Although CT is able to detect some hepatic carcinoid metastases, many lesions were not detected. In contrast with this, angiography was able to demonstrate hepatic metastases even when their size was less than 1 cm. We therefore consider hepatic angiography

essential for evaluation of patients with carcinoid syndrome, and for the management of hepatic carcinoid metastases.

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Selective Mesenteric Vein Catheterization and Plasma Serotonin Determination in Patients with Carcinoid Tumors

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Selective abdominal vein catheterization with blood sampling for serotonin determination was evaluated regarding its use in the diagnosis, location, and characterization of carcinoids. Serotonin was determined in a platelet-poor plasma fraction (PPP) by an enzymatic procedure.

In 5 normal subjects the concentration of serotonin in PPP in the celiac artery, the hepatic vein, and different intestinal and pancreatic veins ranged from 1.2 to 5.4 ng/ml. In 10 patients with carcinoid tumors, the concentration of serotonin in tumor-draining veins was clearly elevated and ranged from 10 ng/ml to 88 ng/ml PPP. 5-HIAA urine levels were false-negative in 4 cases, liver scintiscan was false-negative in 3 cases, and the angiograms were not conclusive in 2 cases.

The technique with plasma serotonin determination in combination with selective catheterization is a useful complement to other investigative techniques in the diagnosis, location, and follow-up of patients with carcinoid tumors.

The carcinoid tumor was first described as a pathologic entity by Oberndorfer in 1907, but it was not until 1954 that it was identified as having the capability to liberate a hormone (serotonin) [1]. It has since been shown that the tumor produces also kallikrein [2] and sometimes polypeptide hormones [3, 4]. It has been suggested that the substances liberated by the carcinoids might prove useful tumor markers [5-8] and thereby facilitate an earlier diagnosis of the tumors. Realization of this idea has

been hampered, however, by the absence of demonstrable significant hormone changes in peripheral blood in cases in which metastatic growth is not extensive.

This report concerns the measuring of serotonin in platelet-poor plasma (PPP) in combination with intestinal vein catheterization [7, 9, 10] for the diagnosis and location of carcinoid tumors.

Methods

Catheterization Technique

With the patient fasting (8-10 hours), simultaneous aortic, caval, and portal vein catheterization with selective intestinal and pancreatic vein catheterization for blood sampling was performed under local anesthesia. The aortic catheter was placed in the celiac artery and the caval catheter in the right hepatic vein. The two catheters were kept in these positions throughout the investigation. Percutaneous transhepatic puncture of the portal vein was performed with a 25-cm long needle sheathed with a polyethylene catheter. The puncture was performed in the right midaxillary line toward the hilum of the liver. The needle was withdrawn and the catheter slowly pulled back until blood could be aspirated without resistance.

After injection of a small amount of contrast medium during fluoroscopy to assure the correct position in a portal vein branch, a guide wire with soft tip was manipulated into the portal vein. The portal catheter was then pushed over the guide wire into the same position after which it was moved to different branches of intestinal and pancreatic

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Fig. 1. Injection into a peripheral branch of the superior mesenteric vein draining the distal ileum. Filling of the ileocolic vein (arrow). Blood sampling sites are identified on this type of phlebogram.

veins. Blood samples for serotonin assay were obtained from 6–12 different intestinal and pancreatic veins. Simultaneously, blood samples were collected from the catheters placed in the celiac artery and the hepatic vein. The sampling sites and the anatomy of the adjacent vessels (Fig. 1) were demonstrated phlebographically and fluoroscopically (see also [10]).

The study was approved by the local ethical committee.

Blood Sampling and Serotonin Assay

For each serotonin determination, 8 ml blood was collected in ice-chilled tubes containing EDTA and ascorbic acid as protective agents. The samples were centrifuged in 2 steps to produce a platelet-poor plasma (PPP), which was used for the subsequent analysis. The number of platelets in our preparation averaged $10 \times 10^9/L$ plasma (normal platelet count $170\text{--}330 \times 10^9/L$ plasma). The plate-

let-poor preparation was applied to a Sephadex® G-10 column, equilibrated, and washed with redistilled water. The serotonin was eluted with 0.5 M formic acid. The serotonin-containing fractions were freeze-dried and the residue was taken up in 0.2 M phosphate buffer.

Serotonin was then converted to tritiated melatonin with the enzymatic procedure described by Saavedra and associates [11], and the melatonin formed was quantitated by liquid scintillation counting. The counts were converted to concentrations in nanograms serotonin/ml platelet-poor plasma with the use of a calibration curve based on the analysis of plasma samples with known amounts of serotonin added. The concentrations were thus corrected for recovery.

Light Microscopy

Tissue specimens obtained at surgery were processed for light microscopic investigation according to the Falck-Hillarp histofluorescence method [12–14] for the intracellular visualization of serotonin.

Materials

Three women and two men, ages 38 to 68 years, with pancreatic gastrinoma were catheterized and blood samples were taken for serotonin determination. None of these patients had any clinical, laboratory, or morphologic symptoms or signs of carcinoid tumors. These 5 patients were used as a reference group.

Ten patients with verified or suspected carcinoid tumors were subjected to the triple catheterization. The patients are referred to as patients I–X and relevant data are given in Table 1.

Peripheral blood samples for serotonin quantitation were obtained from 22 persons without carcinoid and 9 patients with metastatic carcinoids of different stages. The extent of the growth was assessed by arteriography, catheterization with serotonin assay, and in certain cases also by the operative findings.

Results

Serotonin in Blood from a Peripheral Vein

In the 22 normal volunteers the serotonin concentration in PPP from a peripheral vein was 2.9 ± 1.5 ng/ml (range: 0.6–5.8 ng/ml). The concentration in the 9 patients with metastatic carcinoid tumors was 14.8 ± 10.6 ng/ml PPP (range: 6.5–35.1 ng/ml) (Fig.

Table 1. Clinical data of 10 patients with carcinoid tumors at the time of plasma serotonin determination.

Patient	Sex	Age (years)	Primary operation	Primary operation curative	Symptoms at time of serotonin determination	5-HIAA ^a in urine (mol/24h) (normal <80)	Liver ^b scintiscan	Arteriography ^b		Plasma serotonin ^b	
								Intes-tine	Liver	Intes-tine	Liver
I	M	40	—	—	Carcinoid syndrome	839	+	+	+	+	+
II	M	66	Ileocecal resection	Yes	None	36	(+)	+	—	+	—
III	M	73	Ileal resection	Yes	None	203	—	+	+	+	+
IV	M	68	—	—	Weight loss, diarrhea	250	+	+	+	+	+
V	F	46	—	—	Glucagonoma syndrome	23	—	+	—	+	—
VI	F	58	Ileal resection	Yes	Carcinoid syndrome	269	—	—	+	+	+
VII	F	56	Cecal resection	No	None	152	+	—	+	—	+
VIII	F	53	Ileal resection	No	None	113	—	(+)	+	+	+
IX	M	50	Ileal resection	Yes	Carcinoid syndrome	67	(+)	—	+	+	+
X	M	55	Ileal resection	Yes	Diarrhea	61	—	+	+	+	—

^a+, elevated levels; — normal values.

^b+, tumor growth; (+) suspicion of tumor growth; — no evidence of tumor growth.

^cArteriography visualized abnormal vessels in the pancreas.

^dElevated serotonin levels in pancreatic veins.

2). This difference in serotonin concentrations was highly significant ($p < 0.001$).

Serotonin in Blood from Mesenteric Veins

The concentrations of serotonin in PPP in different mesenteric veins in the reference group are given in Table 2. In the celiac artery the concentration ranged from 0.9 to 6.3 ng/ml PPP (mean = 2.3 ± 1.5 ng/ml); in the hepatic vein, from 0.9 to 8.9 ng/ml PPP (mean = 2.4 ± 2.7 ng/ml). In the intestinal area the concentration values ranged from 0.5 to 12.5 ng/ml PPP. The mean values in the various intestinal veins were scattered around 3 ng/ml with no significant differences between them. Ten patients with suspected or verified carcinoid tumors were investigated. Relevant clinical data at the time of the catheterization are summarized in Table 1.

Patient I had had epigastric pains for more than 10 years. He was admitted to hospital because of clinical symptoms of a carcinoid. The concentrations of serotonin in the blood samples obtained in association with the catheterization are given in Table 2. The serotonin concentrations were increased compared to the values in corresponding veins from the controls. The highest values in the

intestinal area were found in the superior mesenteric vein and the ileocolic vein, both of which drained the intestinal area with the known tumor masses. The highest serotonin concentration was measured in the hepatic vein, reflecting prominent carcinoid metastasis in the liver. Subsequent surgical exploration revealed the suspected growths.

Patient II was admitted to the hospital with acute obstruction of the small intestine. At operation an ileal tumor was found and ileocecal resection was performed. The histologic examination revealed a carcinoid tumor. The operation was regarded as curative. At review 1 year after the operation, arteriography suggested metastatic involvement of a mesenteric lymph node and the serotonin concentrations in the veins draining the suspected area were abnormally high (Table 2). Subsequent operation revealed carcinoid in the area in question.

Patient III had a 3-year history of severe abdominal pain, when exploratory surgery was performed. Owing to the finding of tumor in the distal ileum, intestinal resection was performed. Microscopical analysis revealed a carcinoid tumor. The patient was referred to us, and selective vein catheterization combined with serotonin assay was performed 15 months after the first operation. The serotonin concentrations in PPP were clearly elevated in the hepatic vein as well as in the inferior and superior

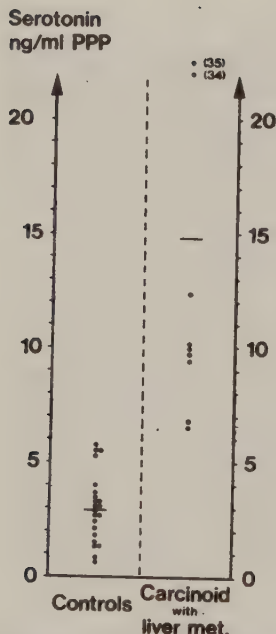


Fig. 2. The distribution of serotonin concentrations in PPP (platelet-poor plasma) from a peripheral vein in 22 normal persons and in 9 patients with metastatic carcinoid tumors.

mesenteric veins and in the gastrocolic vein, indicating carcinoid growth in the intestinal area and in the liver (Table 2). Surgery confirmed the preoperative findings.

Patient IV had for 8 years had abdominal discomfort and episodes of severe diarrhea. Roentgen examination demonstrated an ileal tumor. Owing to a myocardial infarction 1 year previously, operation was postponed. However, the patient developed frequent attacks of partial ileus and was referred to our clinic 2 years after the diagnosis. Serotonin in PPP was increased in the hepatic vein as well as in the intestinal veins, especially in the gastrocolic vein (Table 2). Operation was undertaken to reduce the tumor mass and the ileocecal pool was resected. Metastases were palpated in the liver. A few hours after the operation, cardiac arrest occurred and the patient died.

Patient V had a glucagonoma syndrome and was referred to our department for preoperative localization of the suspected endocrine pancreatic tumor. 5-HIAA levels were normal and the patient had no symptoms referable to a carcinoid tumor.

Hormone assays showed elevated levels of glucagon and insulin from pancreatic veins, as well as a highly significant increase in serotonin concentrations in PPP in the gastrocolic vein (Table 2). The histologic examination of the removed pancreatic tumor revealed a mixed tumor containing serotonin in addition to glucagon and insulin.

Patient VI had been operated on 13 years previously with resection of the distal ileum because of a carcinoid tumor. At the time of the present investigation, the patient had experienced carcinoid symptoms for about a year. The serotonin values not only confirmed the existence of carcinoid tumor growth in the liver, but also conspicuously pointed to the presence of carcinoid tumors in the intestinal area drained by the right colic, the ileocolic, and the jejunal veins. At operation numerous carcinoid nodules were found in the small intestinal mesentery in addition to metastases in the liver and ovaries.

Patient VII presented with a classic carcinoid syndrome and at operation a carcinoid tumor was found in the cecum and resected. Metastases were palpated in the liver. Four years after the first operation venous catheterization with serotonin assay showed an increased hormone concentration in the hepatic vein (Table 2) but not in the other vessels, indicating carcinoid metastases restricted to the liver. At subsequent operation metastases were found in the liver and ovaries.

Patient VIII had had symptoms of epigastric pain and diarrhea for 2 years. Exploratory laparotomy revealed a tumor in the distal part of the ileum as well as metastases in the peritoneum. The distal ileum was resected. Histologic examination showed a carcinoid tumor. Selective vein catheterization with serotonin assay indicated residual serotonin-producing tumor cells in the liver and in the area drained by the ileocolic vein (Table 2). The patient is now followed and a second-look operation is contemplated.

Patient IX had been troubled by abdominal pain for 10 years when exploratory laparotomy revealed a carcinoid tumor in the distal part of the ileum. The tumor was removed and the operation regarded as curative. Postoperatively, the serotonin concentrations in the hepatic vein were, however, severely increased and a slight increment of serotonin was noted also in the ileocolic vein (Table 2). Operation revealed tumor growth in the liver and the peritoneum and thus confirmed what had been suggested by the serotonin levels.

Patient X had experienced abdominal discomfort for 9 years. Exploratory laparotomy revealed a carcinoid tumor of the distal ileum and a few affected lymph nodes, which were removed. At postoperative catheterization the serotonin levels in the intestinal area drained by an ileal vein proved

Table 2. Serotonin concentrations in platelet-poor plasma (ng/ml) in samples obtained from different abdominal blood vessels in the patients with carcinoid tumors (referred to as patients I-X). Control values express mean $\pm$ S.D. in 5 patients without carcinoid tumors.

Vessel	Pat. no.	Controls (n = 5)	I	II	III	IV	V	VI	VII	VIII	IX	X
Celiac artery		2.3 $\pm$ 1.5	34.7	1.1	8.7	10.4	1.0	10.0	8.0	8.9	6.5	3.4
Hepatic vein		2.4 $\pm$ 2.7	88.6	1.4	11.4	42.4	1.0	8.9	26.7	9.6	10.3	3.7
Portal vein		3.6 $\pm$ 4.0	34.3	1.8	9.8	11.6	0.9	9.3	6.1	6.6	6.9	2.3
Splenic vein		2.3 $\pm$ 2.3	35.1	3.0	9.9	14.0	1.3	5.9	6.4	-	5.3	3.1
Inf. mes. vein		2.1 $\pm$ 1.1	-	64.0	16.7	9.8	-	6.0	8.0	2.5	2.5	4.5
Left colic vein		-	-	-	-	-	1.7	-	-	-	-	-
Sup. mes. vein		3.2 $\pm$ 2.8	63.4	1.9	19.1	12.9	1.1	9.9	5.7	6.4	8.1	5.2
Ileocolic vein		5.4 $\pm$ 3.0	62.1	-	-	-	1.6	13.2	4.5	10.7	9.6	4.1
Right colic vein		3.9 $\pm$ 4.0	-	2.2	8.4	10.3	-	29.4	-	-	3.2	2.9
Middle colic vein		3.9 ^a	-	-	-	-	6.2	13.3	-	6.6	-	-
Ileum vein		4.1 $\pm$ 1.6	24.0	-	-	-	-	6.0	3.3	3.3	4.3	15.2
Jejunal vein		3.2 $\pm$ 2.2	51.8	2.7	-	-	1.3	14.4	7.5	9.7	9.0	6.0
Pancreaticoduodenal vein		1.2 $\pm$ 0.4	-	-	-	-	-	15.1	-	-	-	-
Gastrocolic vein		2.6 $\pm$ 2.1	-	-	16.7	31.6	35.9	-	-	-	-	-
Peripheral vein		2.9 $\pm$ 1.5	34.2	2.6	6.5	10.0	1.1	9.2	12.3	6.8	9.6	5.6

^aOnly 1 observation.

high. Arteriography suggested a lesion not only in the region where the serotonin concentrations were high but also in the liver. At the second-look operation a secondary carcinoid was excised from the omentum close to the ileocecal pool, but no tumor was found in the liver parenchyma despite very careful palpation.

Light Microscopic Analysis

Tumor tissue from the 10 carcinoid patients was classified as carcinoid by its typical light-microscopical appearance. In addition, all tumors showed argyrophilia with the Grimelius technique and strong serotonin fluorescence with the Falck-Hil-larp histofluorescence technique.

Discussion

Selective abdominal vein catheterization with blood sampling for determination of serotonin was evaluated regarding its use in the diagnosis, location, and characterization of carcinoid tumors. This procedure for hormone analysis has been used by our group in the diagnosis and location of pancreatic endocrine tumors [9, 15, 16]. This technique has proven capable of detecting poorly vascularized or small tumors difficult or impossible to demonstrate by angiography (see also [10]). The method has proven sensitive enough to identify microscopic lesions, such as islet cell hyperplasia [17].

Progress in the elucidation of the role of serotonin in the causation of different symptoms of the carcinoid disease and the use of serotonin as a tumor marker have been somewhat hampered by the lack of sensitivity and specific methods for quantitation. The analytical methods based on spectrophotofluorometry [18] or bioassay [19] are cumbersome and may not completely distinguish serotonin from other 5-hydroxyindoles. Improved methods for serotonin determination have recently become available, such as radioimmunoassay [20] and enzymatic-isotopic techniques [11]. In this study, we adapted the enzymatic-isotopic methods to meet our requirements and used this adapted technique for serotonin determination in a platelet-poor plasma fraction. The serotonin concentration in peripheral blood in 22 normal volunteers averaged 2.9 ± 1.5 ng/ml PPP. This concentration is in the same range as serotonin levels in PPP previously reported [21-23]. The dispersion between platelet-bound serotonin and free plasma serotonin in our PPP-preparation is not known, but since our preparation contained about 10,000 platelets/mm³ it is possible that a dominating portion of the serotonin determined was platelet-bound. We are investigating the amount of serotonin circulating free in the plasma. The existence of a free serotonin pool has been denied by Kellum and Jaffe [20].

Most carcinoid tumors secrete serotonin in spite of the fact that a relative deficiency of aromatic amino acid decarboxylase may not be uncommon in these tumors [23]. The main purpose of the present study was to develop a procedure for demonstrating

carcinoids, with the aid of selective catheterization and serotonin determination. All the 10 carcinoid patients investigated had elevated serotonin levels in tumor-draining veins. The diagnostic accuracy was thus 100% in these cases and superior to that of other diagnostic techniques. 5-HIAA levels were false-negative in 4 patients (II, V, IX, and X), and liver scintiscan was false-negative in 3 patients (III, VI, and VIII). There are also several well-documented cases in the literature of serotonin-producing carcinoid tumors and carcinoid syndrome in patients with normal 5-HIAA excretion and elevated serum serotonin concentrations [24]. Angiography demonstrated the tumors in the intestine and the liver in most of the cases. In such cases when the angiographic techniques unequivocally showed tumor growth, the serotonin determinations facilitated the classification of the neoplasms as carcinoids. The roentgenologic difficulties in diagnosing primary tumors and metastases of carcinoids are exemplified in patients VI and X. In patient VI serotonin concentrations were increased in the liver and certain bowel veins whereas no bowel tumor masses were revealed with arteriography. At operation, carcinoid metastases were found in the liver and in the omentum. In patient X the angiogram indicated a carcinoid metastasis in the liver. Serotonin values in the hepatic vein were, however, normal, and neither very careful palpation at operation nor examination of liver biopsy specimens verified tumor growth.

The catheterization technique is valuable also for follow-up of patients operated on for carcinoid tumor. Serotonin determination facilitates early detection of any new metastatic growth or rapid expansion of existing tumor masses. It has enabled a relatively early secondary radical operation in cases in which the primary operation had failed to remove all the affected tissue and tumor growth was not too extensive. Selective vein catheterization with blood sampling for serotonin determination is thus advocated for early diagnosis, location of lesions, and reliable follow-up of patients with suspected primary carcinoid tumors or metastases.

Résumé

Le dosage de la sérotonine dans le sang prélevé en des points précis du système veineux abdominal grâce au cathétérisme sélectif a été étudié par les auteurs au plan du diagnostic et de la localisation de la tumeur carcinoïde. Le taux de la sérotonine a été déterminé par une technique enzymatique portant sur une fraction plasmatique plaquettaire particulière (P.P.P.P.).

Chez 5 sujets normaux, la concentration de la

sérotonine dans des échantillons sanguins prélevés au niveau de l'artère coeliaque, de la veine hépatique ?, des veines pancréatiques et de différentes veines de l'appareil digestif s'est située entre 1, 2, 5, 4 ng/ml. Chez 10 malades qui présentaient des tumeurs carcinoïdes cette concentration dans le sang des veines drainant les tumeurs était nettement élevée et variait entre 10 ng/ml et 80 ng/ml. Chez ces mêmes malades 5 dosages de 5 H.I.A.A. urinaire faussement négatif ont été constatés ainsi que 2 scintigraphies hépatiques faussement négatives et 2 angiographies d'interprétation incertaine.

La méthode étudiée se présente donc comme un complément utile des autres méthodes d'explorations permettant de porter le diagnostic de tumeur carcinoïde, de déterminer son siège et de suivre l'évolution des malades porteur de cette lésion.

Abstracto

Se realizó la evaluación del cateterismo selectivo de venas abdominales en relación a su uso en el diagnóstico, localización y caracterización de carcinoides. La serotonina fue determinada en una fracción de plasma pobre en plaquetas (PPP) por un procedimiento enzimático.

La concentración de serotonina en PPP en la arteria celiaca, la vena hepática y en diferentes venas intestinales y pancreáticas osciló entre 1.2-5.4 ng/ml. En 10 pacientes con tumores carcinoïdes la concentración de serotonina en las venas que drenaban el tumor se encontró notoriamente elevada y varió desde 10 mg/ml hasta 88 mg/ml PPP. Los niveles de 5-HIAA en orina fueron negativos falsos en 4 casos, el centelleoescanograma del hígado fue negativo falso en 3 casos y el angiograma fue no conclusivo en 2 casos.

La técnica de la determinación de serotonina en el plasma en combinación con el cateterismo selectivo es un complemento útil de otras técnicas investigativas en el diagnóstico, localización y seguimiento de pacientes con tumores carcinoïdes.

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Temporary Liver Dearterialization in Patients with Metastatic Carcinoid Disease

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The surgical treatment of liver metastases from carcinoid tumors is burdened by a relatively poor symptomatic relief and a high mortality rate. Temporary liver dearterialization, separating the operative trauma from the temporary hepatic occlusion, may have advantages. We have utilized this treatment in 16 patients. The effect of treatment was registered in symptomatic relief, changes in urinary 5-HIAA, serotonin in platelet-poor plasma, and morphologic changes shown by angiography.

Fourteen patients, who underwent only the dearterialization procedure, survived the immediate postoperative period, while 2 patients who had concomitant small bowel resection both died of complications, 1 and 3 months postoperatively, respectively. One patient died, 14 months postoperatively, of the carcinoid disease. All but 1 patient were free from symptoms for at least 6 months. Two patients have had no recurrence of the carcinoid syndrome for 34 and 42 months, respectively. A decrease in urinary 5-HIAA was seen after 6 months in 10 patients, serotonin declined in 7 patients, and angiography showed regression in 7 patients. The results of this study indicate that temporary liver dearterialization is a safe procedure with low mortality and good symptomatic relief from the carcinoid syndrome.

Both primary and secondary liver tumors are chiefly supplied by blood from the hepatic artery, which was first shown by Segall in 1923 [1] and later confirmed by others [2, 3]. Smaller tumors [4] and

the peripheral zone in larger tumors [5], however, also receive a significant blood supply from the portal vein.

This pattern of blood supply led to development of the method of hepatic artery ligation for ischemic treatment of liver tumors [6]. The results of the arterial ligation were generally poor and the treatment did not seem to affect survival [7]. One reason for the insignificant effect is that after hepatic artery ligation collateral circulation develops within a few days [8], and there are at least 26 potential routes for the development of collaterals [9]. These circumstances led to the technique of total hepatic dearterialization, the aim of which is to disrupt all attachments fixing and surrounding the liver with the exception of the hepatic artery and veins, the portal vein, and the common bile duct [10, 11]. With this modification, ischemia increased and development of collaterals was delayed.

In a review, Almersjö et al. [12] found that total hepatic dearterialization as a sole procedure did not prolong survival. Instead, an increase in perioperative mortality and complications were noted as compared to the hepatic artery ligation procedure. The combination of total hepatic dearterialization or hepatic artery ligation with postoperative chemotherapy might be more beneficial [13, 14] and perhaps even prolong survival [12].

The temporary hepatic dearterialization procedure was described in 1974 [10]. The purpose was to minimize the perioperative mortality and complications by separating the occlusion of the hepatic artery from the operative trauma. In addition, the procedure could be repeated and the artery used for infusion chemotherapy and for angiographic controls. In a series of 21 patients, there was no operative mortality and the observed complications

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Table 1. Clinical data on 16 patients with metastatic carcinoids at the time of temporary liver dearterialization.

Patient	Sex	Site of primary tumor	Age at operation	Carcinoid syndrome	Serotonin in PPP (ng/ml)	5-HIAA in urine (μ mol/24 h)	Liver function tests
1	M	Ileum	64	No	17	69	Normal
2	F	Ileum	68	Yes	991	1,220	Normal
3	M	Ileum	72	Yes	16	178	Normal
4	M	Ileum	50	Yes	11	81	Normal
5	M	Ileum	39	Yes	56	223	Elevated
6	F	Ileum	52	Yes	—	2,000	Normal
7	F	Ileum	45	Yes	9	119	Normal
8	M	Ileum	65	Yes	—	—	Normal
9	M	Duodenum	68	Yes	5	283	Normal
10	F	Ileum	60	Yes	50	165	Normal
11	M	Ileum	56	Yes	270	135	Normal
12	F	Cecum	55	Yes	113	595	Normal
13	M	Ileum	72	Yes	69	87	Normal
14	M	Ileum	52	Yes	388	924	Normal
15a	F	Ileum	52	Yes	—	225	Normal
15b	F	Ileum	53	Yes	—	175	Normal
16	F	Ileum	58	Yes	26	54	Normal
Normal range:					<9	<80	

included liver abscesses in 2 patients, arterial aneurysms in 3 patients, bile fistula in 1 patient, and bleeding along the catheter in 1 patient [15].

It has been suggested that the ischemic liver treatment could be of special benefit in patients with metastases from carcinoid tumors because of the possibilities of reducing not only the tumor growth but also the carcinoid symptoms [14, 16]. During the last 10 years, there have been reports on about 25 carcinoid patients treated with hepatic artery ligation or total hepatic dearterialization [16–18]. A reduction of carcinoid symptoms lasting more than 3 months was observed in about 50% of the patients, but there was a mortality rate of about 25% in the immediate postoperative period [16–18].

We have treated 16 patients, suffering from metastatic carcinoid tumors, with temporary hepatic dearterialization. One patient was treated twice, so a total of 17 temporary dearterializations have been performed. This report shows the results as reflected in changes in symptomatology, secretion and excretion of tumor markers (serotonin and 5-hydroxyindoleacetic acid [5-HIAA]), angiographic evaluation of the tumor mass, and survival.

Material and Methods

Patients

Nine men and 7 women, ranging in age from 39 to 72 years, who had carcinoid tumors with liver metastases

were subjected to temporary hepatic dearterialization. Relevant preoperative data are given in Table 1. All patients were treated once, except for patient no. 15, who was operated on twice (15a and 15b in Table 1).

Operative Procedure

The operative technique has been described previously [10]; after careful dissection the only structures attaching the liver were the hepatic artery, the common bile duct, and the portal and hepatic veins.

Two nylon strings were put around the isolated hepatic artery, distal to the gastroduodenal artery. The nylon strings were threaded through 2 catheters which were taken out through separate incisions in the abdominal wall. Cholecystectomy was always performed to avoid gallbladder necrosis after occlusion of the arterial supply. In 2 patients (patients no. 6 and 8), a small bowel resection was done at the same time. The occlusion of the hepatic artery was achieved by pulling the nylon strings when the patients had recovered from the operation, usually 3–4 days. In 2 patients, the arterial occlusion was postponed for about a fortnight because of a carcinoid crisis (patient no. 2) and a suspected liver abscess (patient no. 14). The arterial blood flow was restored after 16 hours by releasing and removing the strings and catheters. A broad spectrum antibiotic was given from the day before arterial occlusion until 1 week after the dearterialization.

- no syndrome
 ▨ recurrence of carcinoid syndrome
 ▩ other treatment
 * second dearterialization

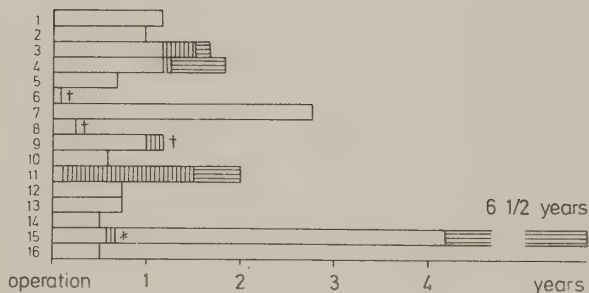


Fig. 1. The follow-up of 16 patients after temporary liver dearterialization: Symptomatic effect and survival.

Angiography

Celiac and superior mesenteric arteriography were performed preoperatively in all patients to evaluate the extent of metastatic tumor growth, to map the arterial anatomy, and to check the patency of the portal vein. Postoperatively, arteriographies were performed at intervals primarily to estimate changes in tumor mass. The completeness of arterial occlusion and the number of overlooked collaterals to the liver were evaluated in 5 patients (patients no. 2, 5, 12, 14, 16) by arteriography performed at the time of occlusion of the hepatic artery.

Biochemistry

Liver function tests were monitored in all patients. Most of the patients were also followed with determination of serotonin in platelet-poor plasma and 5-HIAA in urine.

Serotonin Determination

Blood was collected from the hepatic veins via a caval catheter. Four milliliters of blood was collected in ice-chilled tubes containing EDTA and ascorbic acid as protective agents. The platelet-poor plasma (PPP) was produced by a 2-step centrifugation procedure and the number of platelets in our preparation averaged $10 \times 10^9/\text{liter}$ plasma (normal platelet count $170\text{--}300 \times 10^9/\text{liter}$ plasma). The serotonin determination was performed with high-

pressure liquid chromatography with electrochemical detection [19].

5-HIAA Determination

Urine was collected for 24 hours and the excretion of 5-hydroxyindoleacetic acid (5-HIAA) was measured by a spectrophotometric method [20].

Follow-up

Postoperatively, the patients have been checked every third month with a general examination and biochemical tests. Arteriographies were performed at intervals.

Results

Preoperatively, all patients but 1 (patient no. 1) suffered from the carcinoid syndrome with either flushing or diarrhea or both. The serotonin concentration in platelet-poor plasma (PPP) was above normal in 11 of 13 patients and the urinary excretion of 5-HIAA elevated in 14 of 16 patients so studied before operation (Table 1).

All patients survived the operation and were usually ambulatory on the day after operation (Fig. 1). Temporary occlusion of the hepatic artery was performed 3–4 days after operation in most cases. The procedure was postponed for about a fortnight in patient no. 2 because of a postoperative carcinoid

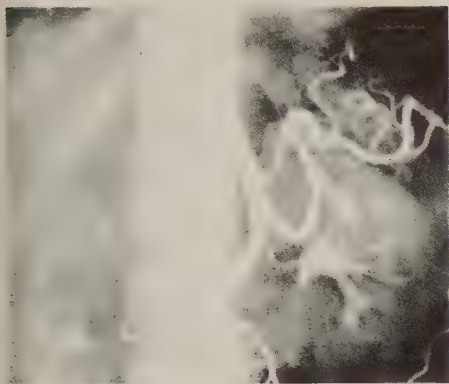


Fig. 2. Coeliac angiography during temporary occlusion of proper hepatic artery. Liver totally deprived of arterial supply. (Patient no. 2).

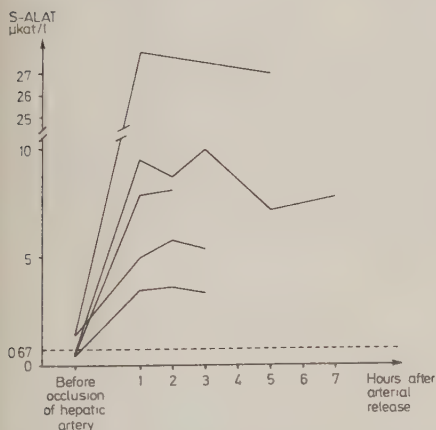


Fig. 3. The S-ALAT changes during the first hours after release of hepatic artery blood flow in the patients (patients no. 2, 5, 12, 14, and 16) in whom hepatic artery occlusion was performed under angiographic control (--- = upper normal limit = 0.67 kat/l).

crisis and in patient no. 14 because of the suspicion of a small liver abscess. The symptoms in connection with the occlusion were mild, consisting of pains, fever, and tiredness. The liver enzyme levels, which in all patients but 1 (patient no. 5) were normal before operation, increased, reaching a maximum a few hours after the release of liver circulation. No clinical signs of hepatic insufficiency

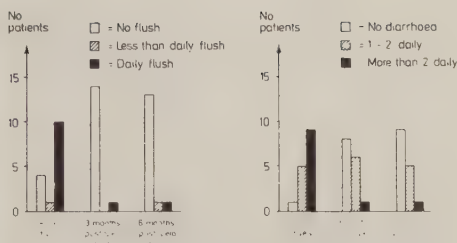


Fig. 4. The effect on flushing and diarrhoea after temporary liver dearterialization in 14 patients subjected to 15 dearterializations and followed for at least 6 months.

were noted, and in all patients the liver enzyme values returned to normal within 6 weeks.

In order to ascertain that a complete dearterialization was achieved, the arterial occlusion was performed under angiographic control in 5 patients (2, 5, 12, 14, and 16). In these patients, no arterial blood supply to the liver could be visualized after occlusion of the hepatic artery (Fig. 2).

To illustrate that the concentration of liver enzymes in serum correlates fairly well with the degree of dearterialization, the values of S-ALAT from the 5 patients occluded under angiographic control are presented (Fig. 3).

Three patients in our series have died (Fig. 1). Two died 1 and 3 months postoperatively, respectively, from complications with liver abscesses and one had in addition a leakage in a bowel anastomosis. These 2 patients had been subjected to a bowel resection at the same time as the preparation for dearterialization was done. The third patient died 14 months postoperatively from the carcinoid disease. The autopsy showed a duodenal primary tumor with metastases to lymph nodes, spleen, liver, and the spine. The 14 patients subjected to 15 temporary dearterializations and surviving more than 3 months experienced an immediate relief of the carcinoid symptoms after the temporary dearterialization. The patients were then followed for 6 months and 8 of them for 12 months. Five patients were observed for 18 months or more (Fig. 1). In the 14 patients in whom 15 temporary dearterializations were performed, the symptom-free period varied from 1 month up to 42 months (Fig. 1). The mean period during which our patients were free of manifestations of the carcinoid syndrome was more than 3 months. Ten patients had daily flushing and 9 had more than two episodes of diarrhoea per day preoperatively (Fig. 4). After 6 months, only 1 patient experienced recurrence of daily flushing and frequent diarrhoea, symptoms which, in fact, debuted one month postoperatively (Figs. 1 and 4).

Table 2. Summary of effects of the temporary dearterialization on metastatic carcinoids.

Patient	Preoperatively			6 months postoperatively			Angiography	12 months postoperatively			Angiography
	Carcinoid syndrome	Serotonin ^a	5HIAA ^b	Carcinoid syndrome	Serotonin	5HIAA		Carcinoid syndrome	Serotonin	5HIAA	
1	No	17	69	No	4	28	Regression	No	2	20	Regression
2	Yes	991	1,220	No	147	131	Regression	No	12	158	Regression
3	Yes	16	178	No	—	170	—	Yes	66	524	No change
4	Yes	11	81	No	16	87	—	Yes	96	128	Progression
5	Yes	56	223	No	19	64	Regression				
7	Yes	9	119	No	—	39	No change	No	15	52	No change
9	Yes	5	283	No	4	63	—	Yes	2	72	Regression
10	Yes	50	165	No	8	182	Regression				
11	Yes	270	135	Yes	259	—	No change	Yes	436	404	Progression
12	Yes	113	595	No	85	142	Regression				
13	Yes	69	87	No	15	69	—				
14	Yes	388	924	No	65	317	Regression				
15a	Yes	—	225	No	—	52	Progression				
15b	Yes	—	175	No	—	—	No change	No	—	—	Progression
16	Yes	26	54	No	26	23	Regression				

^aSerotonin normal value < 9 ng/ml.^b5HIAA normal value < 80 μ mol/24 h.

The concentration of serotonin in PPP from the hepatic vein was measured in 13 patients (Tables 1 and 2). Preoperatively, the levels were above normal in 11 patients, while 1 patient (patient no. 7) had a borderline value and one (patient no. 9) had a normal serotonin concentration. This patient had a carcinoid tumor of foregut origin (Table 1). Six months after operation, the serotonin levels were lower in 7 of 11 patients and unchanged in 4. Of the 7 patients in whom the serotonin concentration was measured 12 months after operation, a value lower than or at the same level as that at the time of operation was reported in 4 patients and an increased value in 3 patients (Table 2).

The level of 5-HIAA in urine was followed in 15 patients and pathological levels were found preoperatively in 13 of them. The temporary dearterialization led to a reduction in 5-HIAA excretion in most patients and, after 6 months, the values were lower than preoperatively in 10 of 13 patients (Table 2). In fact, 7 patients had 5-HIAA excretion values within the normal range 6 months after temporary dearterialization. At 12 months postoperatively, we determined 5-HIAA excretion levels in 7 patients and found that in 4 patients, the levels still were lower than before the operation and that, in fact, 3 patients had a normal urinary 5-HIAA concentration (Table 2).

The angiographic control showed regression and necrosis of the liver metastases after 8 of the 15 operations on the patients surviving more than 3 months (Fig. 5). Four angiograms demonstrated no

change, while 2 showed a progression of tumor growth at the first postoperative angiographic control (Table 2). In 2 patients (patients no. 11 and 15b), a period without observable tumor growth after the operation was followed by a new phase of tumor progression (Table 2).

Discussion

It has been shown that in patients with metastatic carcinoid disease and the carcinoid syndrome, the 5-year survival is about 20–30% [21]. This is in contrast to the common opinion that the carcinoid is a rather benign tumor. Moreover, it is evident that the symptoms of the carcinoid syndrome are very embarrassing and significantly reduce quality of life. It is against this background that we have undertaken the present study to evaluate the efficacy of ischemic liver treatment with temporary dearterialization in palliating symptoms in patients with metastatic carcinoid tumors and in reducing tumor growth.

Liver metastases from carcinoid tumors have been treated with resection [22, 23], enucleation [24, 25], hepatic artery ligation [26], and total hepatic dearterialization [27, 28]. Hepatic artery ligation and total hepatic dearterialization give a good symptomatic result in about 50% of patients treated [16–18], but the operations are followed by a significant mortality rate [16–18]. In the temporary dearterialization procedure, the operative trauma is

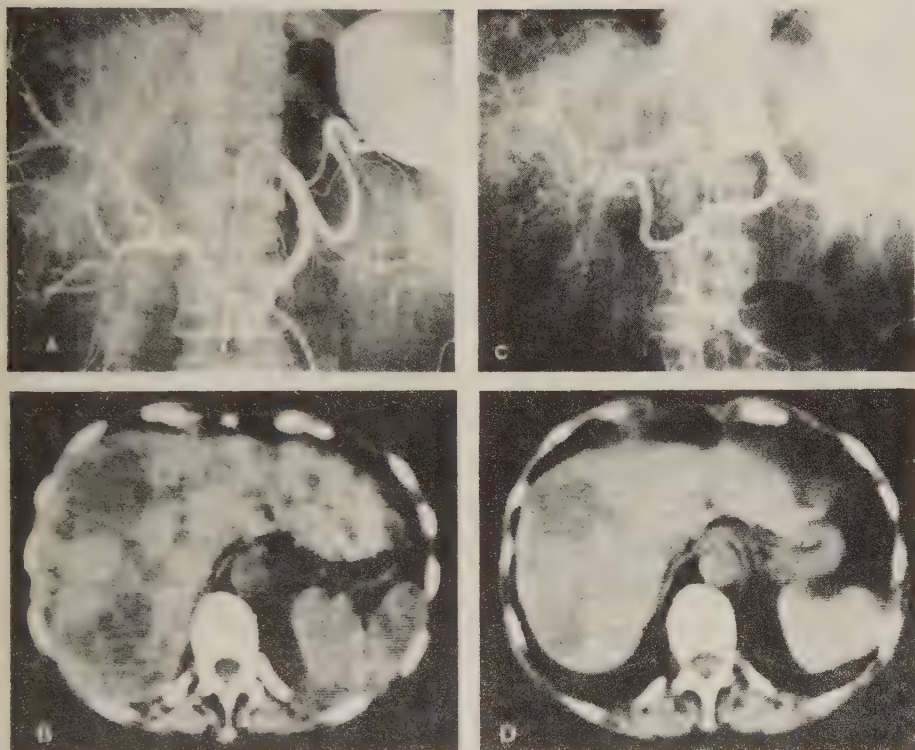


Fig. 5A. Coeliac angiography demonstrates an enlarged liver with intrahepatic arteries displaced by metastases. B. CT-examination the same day as angiography shows widespread metastases. C. Coeliac angiography one year after A shows reduced liver size. Intrahepatic arteries no longer displaced. D. CT-examination one day after C shows markedly reduced size of liver metastases in comparison to B.

separated from the liver cell damage during the occlusion of the hepatic artery, and this seems to have a favorable effect on complications and mortality. In our series, there was no operative mortality among those patients who were only subjected to the liver dearterialization procedure. The 2 early postoperative deaths occurred in those patients in whom bowel resections were performed together with the dearterialization. To minimize the complications and mortality during operation and in the early postoperative period, it is also important that cardiac and respiratory functions be closely monitored so that early treatment of the effects of the potent hormones released from the tumor may be initiated [29].

The effectiveness of the dearterialization is dependent upon a careful dissection to avoid collateral

blood supply to the liver [10]. The lack of collaterals and the completeness of occlusion in the hepatic artery can be checked by angiography, and this procedure is advisable in all doubtful cases.

The dearterialization caused a transient increase in serum liver enzyme levels, but no signs of hepatic insufficiency were observed in our series; this is in accord with many earlier reports [10, 30]. Tolerance to hepatic dearterialization requires, however, an intact portal vein [10, 28].

The palliation of symptoms in our 16 patients after treatment is encouraging and there was a clear improvement after 6 months in 13 patients. Eight patients were followed 12 months, and in this group 4 patients still experienced a good palliation. Two patients who preoperatively suffered from the carcinoid syndrome were after the temporary dearteriali-

zation free of symptoms for 34 and 42 months, respectively. To our knowledge, comparable results have not been reported in the literature.

To evaluate the effect of temporary hepatic dearterialization on tumor mass and growth is more difficult, due to the lack of methods for estimating the tumor volume. Angiography can provide only a crude estimation of the extent of liver metastasis; and after dearterialization, problems arise as to how to differentiate vital tumor tissue with hypovascularity from areas of necrosis [31]. Preliminary data suggest that angiography in combination with computed tomography might improve the accuracy [31]. Neither is urinary excretion of 5-HIAA a good criterion of tumor size [28]. Normal levels do not exclude the possibility of carcinoid tumor growth and, on the other hand, patients with limited tumor mass can have high 5-HIAA levels. Serotonin in blood and plasma has been claimed to be a good tumor marker, especially in patients with carcinoids of midgut origin [32, 33].

In our study, angiography demonstrated regression of carcinoid liver metastasis in about 50% of the cases, and this is at variance with other reports where regression is noticed in a higher percentage [11, 15, 27]. This disparity might be explained by the difficulties in estimating tumor volume on angiograms.

In our hands, serotonin in platelet-poor plasma served as a reliable tumor marker and a good criterion of tumor size and activity [32]. In particular, comparison of serotonin concentration in the individual patients from time to time gives clear indications of tumor decrease or increase. Other substances released from the carcinoids, such as substance P, can probably serve the same purpose [34].

The generally accepted basis for the methods of disrupting blood flow to the liver metastases is that they produce ischemia and thereby necrosis of the metastases [4, 11]. This hypothesis has recently been questioned by Hafström (personal communication) who claims that it is lack of substrate, rather than lack of oxygen, that produces tumor necrosis.

We consider temporary liver dearterialization the method of choice in the treatment of liver metastases from carcinoid tumors. The method combines reasonable security with good palliation of carcinoid symptoms and reduction of the tumor mass.

Résumé

Le traitement chirurgical des métastases hépatiques des tumeurs carcinoides n'entraîne qu'une amélioration peu importante des manifestations symptomatiques. Il reste grevé d'une importante mortalité.

La désartérialisation temporaire du foie pourrait en revanche présenter quelques avantages. Nous l'avons tentée chez 16 malades. L'effet du traitement fut jugé en fonction de l'amélioration des phénomènes symptomatiques, des modifications du taux des 5-HIAA urinaires, du taux de la sérotonine dans le plasma et des modifications morphologiques à l'angiographie.

14 patients qui ont été soumis à ce procédé thérapeutique ont survécus à l'opération, alors que 2 sont morts; le premier un mois et le second trois mois après l'opération qui avait comporté la résection de l'intestin. Sur les 14 survivants, un est mort 14 mois après l'opération de la généralisation du processus tumoral, 13 opérés n'ont présenté aucun symptôme du moins pendant 6 mois, 2 n'ont présenté de récidive qu'après 34 et 42 mois respectivement. Une diminution dans le taux des 5-HIAA urinaires après 6 mois fut constatée chez 10 malades. Le taux de sérotonine s'abaisse chez 7 d'entre eux, cependant que l'angiographie montrait une régression des lésions chez également 7 de ces malades.

Les résultats de cette étude montrent que la désartérialisation temporaire du foie représente un procédé thérapeutique valable car la mortalité opératoire est faible et les symptômes dus à l'origine carcinoidale du processus tumoral régressent nettement.

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EMBOLIZATION OF THE LIVER IN THE MANAGEMENT OF METASTATIC CARCINOID TUMORS

Short title: Embolization of metastatic carcinoids.

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ABSTRACT

Eight patients with metastatic carcinoid tumors and the carcinoid syndrome were treated with gelatin foam embolization of the hepatic arterial tree. The aims were to reduce the tumor mass in the liver and to eliminate the carcinoid syndrome. The effects of the treatment were judged from arteriograms, CT-scans and the levels of serotonin in blood and 5-HIAA in urine, as well as from the clinical symptoms. The mean follow-up time was 12.5 months. In all patients the liver tumor mass was reduced after embolization and this reduction persisted for at least 6 months in 7 patients. After treatment reduced serotonin levels in blood was measured in 4 patients and reduced 5-HIAA levels in urine in 7 patients. In 5 patients the carcinoid syndrome disappeared after embolization but after 6 months 2 of these 5 patients had regained symptoms. Adverse reactions were minor consisting of a slight fever, reversibly increased serum levels of liver enzymes and abdominal pain. In our experience the hepatic embolization is a simple and safe method of giving relief from the carcinoid syndrome.

KEY WORDS: Carcinoid tumor; carcinoid syndrome; liver metastases; hepatic embolization; serotonin.

INTRODUCTION

Malignant endocrine gastrointestinal tumors disable patients both with the tumor burden as such with general cachexia, and with the widespread effects of the hormones released from the tumor. Therefore treatment of these patients should aim at achieving both tumor reduction and a decrease in the synthesis and release of active substances from the tumor tissue.

Cytotoxic drugs such as streptozotocin, adriamycin or 5-fluorouracil have been disappointing in the treatment of intestinal endocrine tumors (1, 2) whereas this treatment has been of some benefit in selected cases with endocrine pancreatic tumors (2). The fact that liver tumors chiefly are supplied by blood from the hepatic artery (3, 4, 5) lead to the development of different methods of hepatic artery ligation for ischemic treatment of liver metastases. This principle was, however, not effective in relieving symptoms and prolonging survival until the temporary hepatic dearterialization procedure was introduced in 1974 (6). This procedure has recently been evaluated in the treatment of metastatic carcinoid disease and was found to be a safe procedure with low mortality which provides good symptomatic relief from the carcinoid syndrome (7). Embolization of the hepatic artery also creates an ischemic milieu in the liver and was tried in the treatment of malignant endocrine tumors by Allison and collaborators (8, 9, 10).

This study comprises 8 patients suffering from metastatic carcinoid tumors treated with gelatin foam powder embolization of the hepatic arterial tree. The patients were either previously treated with temporary liver dearterialization and had reappeared carcinoid symptoms or they were for other reasons unsuitable for the dearterialization procedure. This report presents the effects of embolization on symptomatology, on the secretion and excretion of serotonin and 5-hydroxy-indoleacetic acid (5-HIAA) and on the tumor mass. A preliminary report on the embolization technique has been published recently (11).

MATERIAL AND METHODS

Patients

Six men and 2 women ranging in age from 52 to 73 years, who had carcinoid tumors of ileal origin with liver metastases were subjected to gelatin foam powder embolization of the hepatic arterial tree. Relevant patient data are given in Table I. All patients had undergone cholecystectomy to prevent gallbladder necrosis following the embolization. All patients were embolized once except for patient no. 6, who was treated twice.

Table I. Clinical data on the patients at the time of hepatic embolization.

Patient	Sex	Age	Previous treatment	Reason for embolization	Carcinoid syndrome
1	M	51	Small bowel resection. Temporary dearterialization	Previous temporary dearterialization	Yes
2	M	70	Ileocecal resection	Poor general condition	Yes
3	F	68	Small bowel resection	Poor general condition	Yes
4	M	56	Small bowel resection. Temporary dearterialization	Previous temporary dearterialization	Yes
5	M	62	Small bowel resection. Liver resection	Poor general condition	Yes
6 a	M	52	Temporary dearterialization. Small bowel resection	Previous temporary dearterialization. Poor general condition	Yes
6 b	M	52	Temporary dearterialization. Small bowel resection. Embolization	Previous embolization without sufficient effect	Yes
7	M	73	Ileocecal resection. Temporary dearterialization	Previous temporary dearterialization. Poor general condition	Yes
8	F	58	Ileocecal resection. Temporary dearterialization	Previous temporary dearterialization	Yes

Embolization procedure

The patients were starved for 12 h before the embolization and were given 1 mg atropine as premedication. Two hours before the procedure 1 g of cefoxitin (Mefoxitin[®]) was administered.

Due to the risk of liberation of vasoactive substances from the tumor during the procedure, very careful monitoring was carried out according to the principles described for carcinoid patients by Törnebrandt et al (12).

The hepatic artery was catheterized via the left brachial artery with a 5-F polyethylene catheter (ID/OD 1.1/1.6 mm). Before embolization a liver angiogram was done to show patency of the portal vein. Depending on the vascular anatomy, the catheter was then placed in the proper hepatic artery or selectively into the right and left hepatic arteries when the embolization was performed. One ml of dry gelatin foam powder (Spongostan; Ferrosan International, Copenhagen, Denmark) was aspirated into a 10 ml syringe and mixed with 9 ml of 60 % contrast medium and 1 g cefalotin (Keflin[®]). After shaking the mixture a few minutes it was slowly injected through the catheter. Under fluoroscopic control the reduction of flow could be demonstrated. Care was taken not to overfill the injected artery. When peripheral stagnation of contrast medium was seen, the injection was interrupted for about 5 min. If repeated injections showed totally interrupted flow the treatment was considered complete and a control angiogram was performed. After the procedure the patient was carefully monitored in the surgical ward.

Angiography and computed tomography

Liver angiograms were performed on our patients before embolization and at intervals afterwards. The angiograms were used to estimate the tumor mass, by analyzing the distribution, size and degree of vascularity of the metastases according to the principles described by Sako et al (13).

Computer tomography (CT) scans were evaluated before and after intravenous bolus contrast administration.

Biochemistry

Serotonin determination in platelet-poor plasma (PPP) and whole blood was performed according to the procedure described by Nobin et al (14) and 5-HIAA in urine was measured by a spectrophotometric method (15). Liver function tests were monitored in all patients.

Follow-up

The patients were checked after 1 and 3 months and then every third



Fig 1. The arterial circulation in the liver before (a), immediately after (b), and 1 month after (c) embolization (patient no 7).



month after the embolization with a general examination, biochemical tests, arteriography and computed tomography. One year after the embolization the investigations were undertaken at 6 month intervals. The mean follow-up time was 12.5 months ranging from 3 to 30 months.

RESULTS

The embolization procedure interrupted the arterial circulation in the liver in all patients (Figs 1 a and b). Arteriography 1 month after treatment showed restored arterial liver circulation (Fig 1 c).

In all patients the embolization caused abdominal discomfort and nausea lasting for up to 3 h. Febrile reactions ($38.5-39^{\circ}\text{C}$) were generally observed and lasted for 2-14 days. Fluctuations in circulatory or respiratory functions, which could be ascribed to the release of vasoactive substances from the tumor tissue, were not registered. No serious delayed complications such as derangement of liver functions, local abscess formation or septicemia occurred.

Hepatic function, as estimated by serum levels of liver enzymes, was normal in all patients before embolization and it was rapidly but reversibly affected by the procedure (Fig 2). Within 12 days after embolization the serum levels of the liver enzymes had returned to normal.

Before the embolization all patients suffered from the carcinoid syndrome with daily flushing and/or diarrheas. The treatment resulted in the immediate disappearance of the syndrome in 5 patients (Fig 3). In the remaining 3 patients the embolization procedure had no obvious effects on the symptoms. Not even the repeated embolization in patient no 6 resulted in any subjective palliation (Fig 3). In 2 patients (pat no 6 and 7) the carcinoid symptoms were aggravated in spite of treatment and both patients died from general cachexia 5 and 12 months after the embolization (Fig 3). Three months after embolization the 5 patients who responded to the treatment were still free from the carcinoid syndrome but after 6 months the symptoms reappeared in 2 of these 5 patients. One patient was still free of obvious carcinoid symptoms 2.5 years after the embolization.

The effects of the embolization procedure on the extent of tumor mass in the liver are presented in Table II. All patients had widespread metastatic growth in the liver before the treatment. Five patients had metastases constituting more than 75 % of the liver volume. After the embolization there was a reduction in metastatic extent in all patients which persisted for at least 6 months in 7 patients (Figs 4 a and b). The estimations of tumor growth in the liver were performed in the angiograms and the computed tomography of the liver did not add any significant information.

One to 3 months after the embolization the concentration of serotonin in PPP was substantially reduced in 4 patients (no 1, 2, 5 and 7) (Table II) whereas increased serotonin levels in PPP were measured in the remaining 4. After 6 to 12 months the serotonin concentrations in PPP remained low in three patients (no. 1, 2 and 5) while an increase was noticed in 1 patient (no 7). In the 4 patients with elevated serotonin levels in PPP 1 to 3 months after treatment a return to the serotonin concentrations measured before treatment was observed. Serotonin in whole blood was unchanged in all but 1 patient (no. 5). 5-HIAA in urine was reduced in all patients but one (no 6) and in most cases with more than 50 % (Table II).

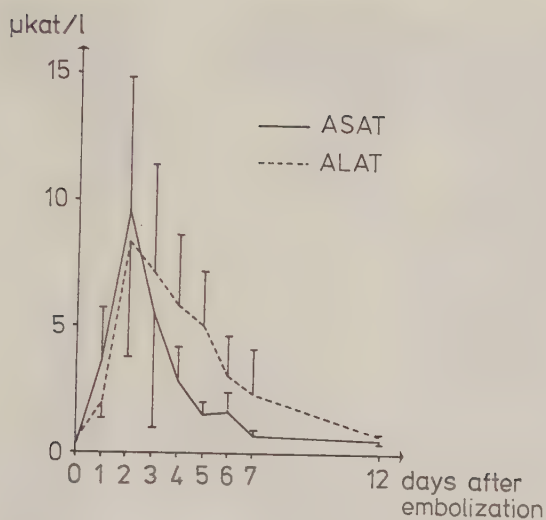


Fig 2. The S-ASAT and S-ALAT changes 1-12 days after embolization. Upper normal limit = 0.67 μ kat/l. Values represent mean $\pm$ SEM.

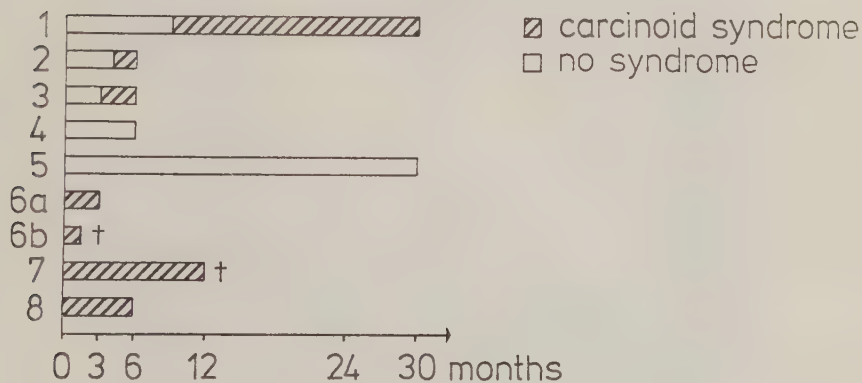


Fig 3. Symptomatic effect and survival after hepatic embolization.

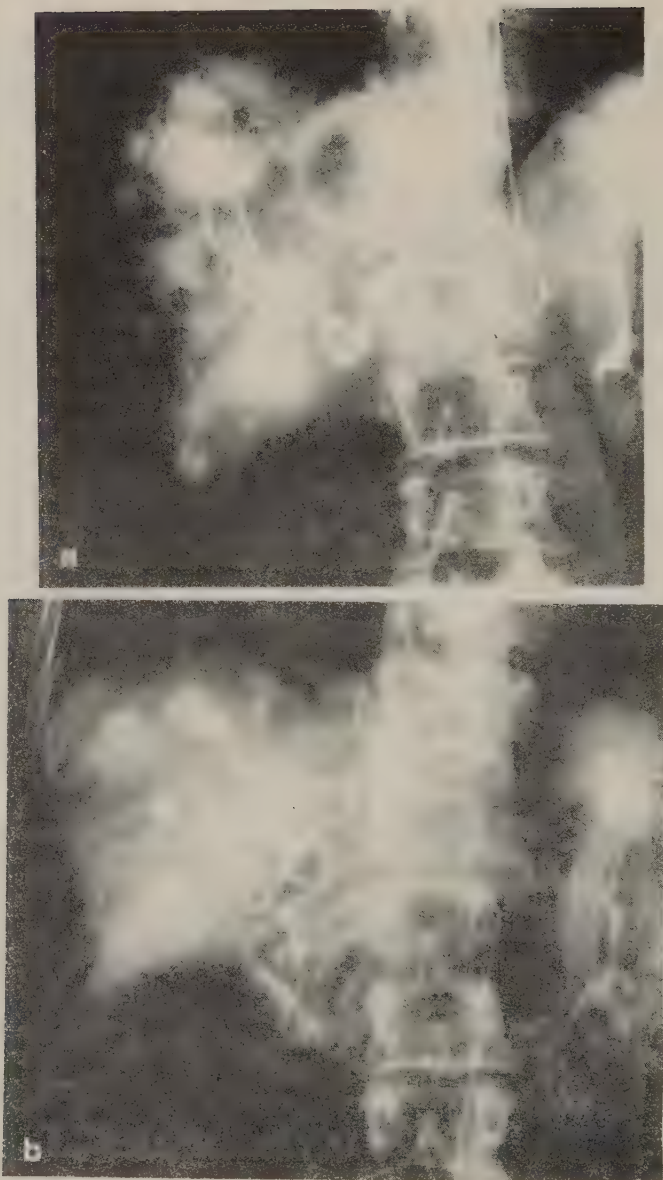


Fig 4. The angiographic appearance of liver metastases before (a) and 6 months after (b) embolization (patient no 4).

DISCUSSION

In the treatment of patients with metastatic carcinoid tumors and the carcinoid syndrome several methods have been used. Most reports, however, contain only a few cases or are collected reviews of the literature (16, 17, 18). In several studies no adequate tumor classification is reported and the site of the primary tumor is in some cases not known. A correct classification is very important and should be the base for treatment. This is exemplified by the fact that some pancreatic endocrine tumors are sensitive to chemotherapy while ileal endocrine tumors are not. The classification should ideally be based on the site of origin, the histopathological features, the immunocytochemical spectrum and the clinical symptoms in the particular patient. We have in the present study treated a group of patients with similar and well defined endocrine tumors. The primary tumors were all located in the ileum, and the morphological and immunocytochemical characteristics were almost identical. In addition, all tumors were malignant and gave rise to the carcinoid syndrome.

In this paper we report our experience with gelatin foam embolization of liver metastases from ileal endocrine tumors. Many different materials have been used in the embolization procedure from a variety of autologous substances to artificial materials (10). The gelatin foam is readily available and relatively safe to use. It has a temporary effect, and thus presumably prevents collaterals to develop, and therefore the treatment can be repeated if necessary.

To avoid irreversible liver damage we consider it important to investigate the patency of the portal vein before embolization. It is also important to place the embolizing catheters as selectively as possible to avoid the unintentional embolization of adjacent organs.

The risk of gallbladder necrosis after embolization or other ischemic treatment of the liver is a controversial question (9, 19, 20, 21). So far, in the light of the risk of posttraumatic gallbladder necrosis, our policy has been to perform a cholecystectomy on the patient before the embolization procedure. In addition, the cholecystectomy gives the surgeon the opportunity to take tumor tissue for optimum classification by cytochemistry and also, by palpation and inspection, to estimate the extent of tumor growth in the abdomen.

Our main criteria for treating patients with malignant endocrine tumors with embolization are either that we know from previous surgical intervention that another surgical procedure like temporary dearterialization or liver resection would be too difficult or risky, or that the patient's general condition is so poor that surgery is not feasible. Due to this our group of patients is selected, which makes it difficult to compare the results with other reports on embolization (9). In spite of this negative selection, several of our patients benefitted to a large extent for the treatment and in 5 patients the

carcinoid syndrome disappeared. In addition, a significant reduction in tumor mass was achieved in all patients. As we have not had any serious complications with embolization, this can be the treatment of choice for patients whose general condition excludes surgical treatment. The return of the carcinoid syndrome in this group of patients can probably be overcome with repeated treatment. It might be of value even to repeat the embolization within 1 month to boost the effect.

In the diagnosis and follow-up of the carcinoid tumor and syndrome no specific laboratory tool is available. The level of 5-HIAA in urine has been claimed to be valuable (22) but other studies have failed to support this (23). In foregut and hindgut tumors we have shown (24) that 5-HIAA in urine can be normal despite liver metastases. To evaluate the effect of temporary liver dearterialization we found (7) that both 5-HIAA in urine and serotonin in platelet-poor plasma could be used. In this series, 5-HIAA in urine was reduced after treatment in all but 1 patient and thus correlated fairly well with the extent of tumor growth but probably to a minor extent to the symptoms of the carcinoid syndrome. Serotonin in PPP and whole blood did not change uniformly. This might be explained by the assumption that serotonin in PPP more reflects the amount of substance release from the tumor. In most patients, the levels of serotonin in PPP was reduced after the embolization, but in some cases an increase was recorded in spite of disappearance of the carcinoid syndrome and reduction in tumor mass. This could be explained by the facts that it is not only serotonin that is responsible for the symptoms and by difficulties in estimating tumor mass from angiograms. Thus, kinins and other peptides have been suggested to play an important role in the carcinoid syndrome (25, 26, 27, 28, 29, 30).

Ischemic treatment of liver metastases can also be obtained by temporary liver dearterialization (16). We have achieved good results in a series of 16 patients with metastatic ileal endocrine tumors (7) concerning relief of symptoms and tumor reduction with this treatment. Embolization is compared to the dearterialization procedure in our patients less successful, but it is important to remember that our patients subjected to embolization were generally worse in their condition. Our current policy is to use the surgical dearterialization if the patient's general condition and previous surgical history so permits. If not, the embolization is performed.

In summary, if temporary liver dearterialization is not possible, we regard embolization of the liver in patients with metastatic endocrine tumors as a valuable complement to other treatment modalities. The embolization procedure is a simple and safe method which provides relief of symptoms without serious complications. Repeated treatments to magnify the therapeutic effects are advisable.

Table II. Biochemical data and tumor extent before and after treatment with embolization of liver metastases.

Patient	Carcinoid syndrome after embolization	Serotonin in PPP (ng/ml)		Serotonin in whole blood (ng/ml)		5-HIAA in urine (μmol/24 h)		Tumor extent in the liver ^a	
		Before	After	Before	After	Before	After	Before	After
		1-3 mo	6-12 mo	1-3 mo	6-12 mo	1-3 mo	6-12 mo	1-3 mo	6-12 mo
1	No	55	25	804	807	129	89	>75%	<25%
2	No	503	231	-	2 100	1 200	-	25-50%	<25%
3	No	8	39	1 022	1 201	2 075	1 040	>75%	<25%
4	No	5	32	869	801	480	170	50-75%	50-75%
5	No	127	16	437	107	128	33	50-75%	25-50%
6a	Yes	30	76	1 375	1 124	1 060	1 095	25-50%	<25%
6b	Yes	36	70	1 662	1 964	-	-	>75%	50-75%
7	Yes	39	5	501	533	1 012	179	>75%	50-75%
8	Yes	9	70	1 167	1 117	904	-	>75%	50-75%
Normal range		male 2+1 female 2+1	male 124+13 female 103+15	<80					

^a Estimated by analysis of the distribution, size, and degree of vascularity of the metastases (13).

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